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Therapeutic Effects of Xanthine Oxidase Inhibitors: Renaissance Half a Century after the Discovery of Allopurinol

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Abstract

The prototypical xanthine oxidase (XO) inhibitor allopurinol, has been the cornerstone of the clinical management of gout and conditions associated with hyperuricemia for several decades. More recent data indicate that XO also plays an important role in various forms of ischemic and other types of tissue and vascular injuries, inflammatory diseases, and chronic heart failure. Allopurinol and its active metabolite oxypurinol showed considerable promise in the treatment of these conditions both in experimental animals and in small-scale human clinical trials. Although some of the beneficial effects of these compounds may be unrelated to the inhibition of the XO, the encouraging findings rekindled significant interest in the development of additional, novel series of XO inhibitors for various therapeutic indications. Here we present a critical overview of the effects of XO inhibitors in various pathophysiological conditions and also review the various emerging therapeutic strategies offered by this approach.

I. Introduction, Historical Background

Allopurinol, or 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one, was one of the crown jewels of the venerable drug discovery program at Burroughs Wellcome that started in 1940s and culminated by the awarding of a 1988 Nobel Prize in Physiology and Medicine to Gertrude B. Elion and George H. Hitchings, shared with British scientist James W. Black, for “discoveries of important principles for drug treatment.” An excellent overview of this effort, which yielded, in addition to the xanthine oxidase (XO)[1] inhibitor allopurinol, block-buster drugs such as acyclovir, trimethoprim, and the early antineoplastic compounds thioguanidine and 6-mercaptopurine (6-MP), can be found in the Nobel lectures by Elion and Hitchings and elsewhere [Hitchings and Elion, 1963;Elion, 1988 (http://nobelprize.org/medicine/laureates/1988/elion-lecture.pdf), 1993]. As they recount, the program grew up out of a very general notion that synthetic analogs of the purine and pyrimidine bases can interfere with nucleic acid biosynthesis. They soon found antibacterial activity for multiple compounds, some of which were tested at Sloan-Kettering Institute for their anticancer properties. 6-MP emerged as having very high activity against leukemia. These

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[1]Abbreviations: XO, xanthine oxidase; 6-MP, 6-mercaptopurine; XDH, xanthine dehydrogenase; XOR, xanthine oxidoreductase; NO, nitric oxide; ROS, reactive oxygen species; UW, University of Wisconsin; CHF, chronic heart failure; NOS, nitric-oxide synthase; nNOS, neuronal NOS; SHR, spontaneously hypertensive rat; AHPP, 4-amino-6-hydroxypyrazolo[3,4-*d*]pyrimidine; BOF-4272, (+/−)-8-(3-methoxy-4-phenylsulfinylphenyl) pyrazolo[1,5-*a*]-1,3,5-triazine-4(1*H*)-one; Y-700, 1-[3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1*H*-pyrazole-4-carboxylic acid.

compounds rapidly progressed into clinical trials and culminated in regulatory approval in 1953, propelled by a desperate need for new treatments, especially for acute leukemia in children, which were limited at the time to methotrexate and steroids. This project ultimately led also to the discovery of allopurinol, when thiouric acid was identified as a major 6-MP metabolite generated by XO.

Inhibition of XO was thought to inhibit oxidation of 6-MP and potentiate the antitumor properties. Because XO was one of the test enzymes in the early experiments in the laboratory, several nontoxic XO inhibitors, including a hypoxanthine analog, allopurinol, were available to directly confirm this suggestion. It was known that XO is involved in formation of uric acid from xanthine and hypoxanthine **(**Fig. 1). Thus, subsequent experiments showed effective control of serum and urinary uric acid by allopurinol (along with the major metabolite, oxypurinol) and its future potential for the treatment of hyperuricemia (although it took a number of years to establish the detailed mechanism of drug action and its safety profile). Although the XO inhibitor discovery programs at Burroughs Wellcome continued for many years, none of the subsequent compounds could surpass allopurinol for in vivo efficacy and tolerance. Allopurinol was approved by the Food and Drug Administration in 1966 for treatment of gout and remains a mainstay in the therapy of primary and secondary hyperuricemia. The mechanism relates to the inhibition of XO-catalyzed formation of uric acid from hypoxanthine and xanthine.

An increasing number of researchers during the past decade have also suggested that XO plays and important role in various forms of ischemic and other types of tissue and vascular injuries, inflammatory diseases, and chronic heart failure (reviewed in Harrison, 2002, 2004; Berry and Hare, 2004) (Tables 1–4). Allopurinol and its active metabolite oxypurinol showed beneficial effects in the treatment of these conditions both in experimental animal models and in small-scale human clinical trials. Although some of the beneficial effects of these compounds go beyond inhibition of XO, these studies generated renewed interest in the development of additional, novel series of XO inhibitors for various therapeutic indications (overview in Borges et al., 2002). The goal of this article is to give a critical overview of the effects of XO inhibitors in various forms of tissue injury and also to review the novel emerging therapeutic strategies offered by this promising approach.

II. The Structure and Molecular Biochemistry of Xanthine Oxidoreductase

Xanthine oxidase (EC 1.1.3.22) and xanthine dehydrogenase (XDH) (EC 1.17.1.4) are interconvertible forms of the same enzyme, known as xanthine oxidoreductase (XOR). The enzymes are molybdopterin-containing flavoproteins that consist of two identical subunits of approximately 145 kDa. The enzyme from mammalian sources, including man, is synthesized as the dehydrogenase form, but it can be readily converted to the oxidase form by oxidation of sulfhydryl residues or by proteolysis. Mechanistic studies of XO and related work on the electron transfer processes has been reviewed (Hille, 1996; Harrison, 2002, 2004); the latter topic also remains a very active area of investigation (Canne et al., 1999; Caldeira et al., 2000; Eger et al., 2000; Enroth et al., 2000; Truglio et al., 2002; Kuwabara et al., 2003; Okamoto et al., 2004). A majority of the recent reaction pathways for XO catalytic transformations are based on the crystal structure of the active site of aldehyde oxidoreductase, as determined by Huber and coworkers (Romao et al., 1995). Both enzymes belong to a molybdenum hydroxylase family as mentioned above, are structurally similar, and have identical X-ray absorption spectra indicative of the same ligand environment and coordination geometry around molybdenum center. The crystal structures of XOR in the two forms, dehydrogenase and oxidase, have been solved after successful crystallization of both forms of the enzyme, to clarify the structure-based mechanism of conversion (Eger et al., 2000; Enroth et al., 2000; Truglio et al., 2002; Kuwabara et al., 2003; Okamoto et al., 2004; Godber et al., 2005) (Fig.

2). The active form of the enzyme is a homodimer of molecular mass 290 kDa, with each of the monomers acting independently in catalysis. Each subunit molecule is composed of an N-terminal 20-kDa domain containing two iron sulfur centers, a central 40-kDa FAD domain, and a C-terminal 85-kDa molybdopterin-binding domain with the four redox centers aligned in an almost linear fashion (Fig. 2). The hydroxylation of xanthine takes place at the molybdopterin center, and the electrons thus introduced are rapidly transferred to the other linearly aligned redox centers. For a more detailed overview of the structure and function of XOR see Harrison (2002, 2004).

XOR is widely distributed throughout various organs including the liver, gut, lung, kidney, heart, and brain as well as the plasma. It is generally accepted that the enzyme normally is present in vivo as an NAD-dependent cytosolic dehydrogenase (XDH), incapable of reactive oxygen species production. Most investigators agree that XDH activity converts by sulfhydryl oxidation or limited proteolysis to an oxidase that produces superoxide and hydrogen peroxide. It is worthwhile to note, nevertheless, that both XO and XDH can oxidize NADH, with the concomitant formation of reactive oxygen species (Zhang et al., 1998a;b; Sanders and Massey, 1999). Physiologically, XO and XDH participate in a variety of biochemical reactions including the hydroxylation of various purines, pterins, and aromatic heterocycles, as well as aliphatic and aromatic aldehydes, thereby contributing to the detoxification or activation of endogenous compounds and xenobiotics. One of XOR's primary roles is the conversion of hypoxanthine to xanthine and xanthine to uric acid (see Fig. 1). Inherited XOR deficiency leads to xanthinuria and a characteristic multiple organ failure syndrome characterized by the deposition of xanthine in various tissues. The detailed biochemistry of XO and XDH conversion of XDH to XO has been subject to several reviews and research papers (Nishino, 1994; Nishino et al., 1997, 2005; Pritsos, 2000; Borges et al., 2002; Ilich and Hille, 2002; McManaman and Bain, 2002; Meneshian and Bulkley, 2002). It is interesting to note that recent work has shown that XO is regulated on the transcriptional and post-transcriptional levels (Hoidal et al., 1997; Terada et al., 1997; Hassoun et al., 1998; Page et al., 1998; Xu et al., 2000; Ghio et al., 2002). For instance, XO is phosphorylated in hypoxic endothelial cells via p38 MAP kinase and casein kinase II, and this process may be necessary for the activation of the enzyme during hypoxia (Kayyali et al., 1998). In a recent study McNally et al. (2005) demonstrated that the endothelial xanthine oxidoreductase protein expression is regulated by hydrogen peroxide and calcium.

In the mid-1970s, it was observed that various hepatotoxic agents, such as halothane and alcohol, induce the systemic release of XO from the liver (Giler et al., 1976, 1977; Ghio et al., 1977; Zima et al., 1993). Initially, it was considered that circulating XO could be used as a sensitive marker to quantitate liver injury. Subsequent work by Freeman and colleagues demonstrated that circulating XO is not only a marker of hepatic and intestinal damage, but it can also act as a circulating mediator that is responsible for remote organ injury in a variety of pathophysiological conditions including hepatic ischemia and reperfusion, hemorrhagic shock, atherosclerosis, and sickle cell disease (Yokoyama et al., 1990; Tan et al., 1993b, 1995b, 1998; White et al., 1996; Radi et al., 1997; Houston et al., 1999; Aslan et al., 2001). Circulating XO activity has also been detected by other groups during thoracoabdominal surgery, intestinal ischemia-reperfusion, skin burn, liver transplantation, and hind limb ischemia and reperfusion (Terada et al., 1992; Poggetti et al., 1992; Nielsen et al., 1994; Burton et al., 1995; Pesonen et al., 1998). Circulating XO has also been demonstrated in human ischemia-reperfusion injury, during an aortic cross-clamp procedure (Tan et al., 1995). It appears that circulating XO binds to glycosaminoglycans on the surface of endothelial cells, where it acquires somewhat modified kinetic characteristics (Radi et al., 1997). Endothelial cell-bound XO continues to produce oxidants, which can trigger endothelial dysfunction, and thereby contribute to organ injury in remote organs such as the lung (Radi et al., 1997). This circulating and depositing XO appears to be more important in the pathogenesis of endothelial injury compared with the

XO constitutively contained in the endothelial cells, which appears to be quite low (Panus et al., 1992; Radi et al., 1997).

It is important to note that many differences exist between the XDH/XO system of various experimental animals and the XDH/XO system present in humans (Sarnesto et al., 1996; Kinnula et al., 1997; Rouquette et al., 1998; Linder et al., 1999; Pritsos,2000). Nevertheless, both the conversion of XDH to XO, and the presence of circulating XO have been confirmed in human studies. It will be important, throughout the current article, to keep in mind that findings obtained in experimental models do not always or necessarily transfer to the human conditions (see also below, for examples of specific disease conditions).

III. Xanthine Oxidase-Derived Superoxide as Part of a Complex Oxidant and Antioxidant System

XO-derived superoxide exerts its actions in the overall context of various endogenous oxidant and antioxidant systems. For example, nitric oxide (NO) can act as an endogenous suppressor of XO activity (Rinaldo et al., 1994; Fukahori et al., 1994; Hassoun et al., 1995; Ichimori et al., 1999; Godber et al., 2000; Kinugawa et al., 2005; see also section V.A. for more details). Because in many pathophysiological conditions there is an impairment of endogenous NO production (e.g., atherosclerosis reduces endothelial NO production), a reduced level of the tonic, NO-mediated suppression of XO may actually lead to increased superoxide generation and pathophysiological positive feed-forward cycles. At the same time, there may also be an XO-derived superoxide dependent tonic suppression of NO synthase activity, which may lead to an enhancement of NO production in response to XO inhibition in vivo (Terada et al., 1997a,b).

There is some evidence that XO can catalyze the reduction of nitrite and nitrate (normally the decomposition products of NO) back to NO (Millar et al., 1998; Zhang et al., 1998b; Godber et al., 2000; Millar et al., 2002). These activities are more prominent under acidic conditions and may contribute to a pathophysiological enhancement of NO generation in ischemic or hypoxic tissues.

The time course of XO-derived superoxide production may also depend on the nature of the chemical environment. For instance, there is some in vitro evidence that oxidative stress can inactivate the activity of XO (Anderson et al., 1995; Houston et al., 1998), but the significance of this mechanism (if any) in vivo is unclear.

XO-derived superoxide can rapidly react with NO or nitrosothiols in its vicinity to form the cytotoxic oxidant species peroxynitrite (Trujillo et al., 1998), which can lead to a feedback inhibition of the enzyme (Houston et al., 1998; Godber et al., 2001), as well as to a variety of oxidative and nitrosative injury to proteins, lipids, and DNA in the vicinity of XO (Trujillo et al., 1998; Sawa et al., 2000). It is conceivable that after binding of circulating XO to the endothelium, XO-derived superoxide can combine with endothelially derived NO (produced by the endothelial NO synthase), and the subsequent formation of peroxynitrite and the activation of downstream pathways of cell injury can lead to endothelial and tissue injury in various pathophysiological conditions (White et al., 1996; Radi et al., 1997; Pesonen et al., 1998; Aslan et al., 2001; Desco et al., 2002; Szabó et al., 2002a,b, 2004; Pacher et al., 2002a,b; 2003a,b; 2005a;b; Obrosova et al., 2005; Ungvári et al., 2005).

We must also put uric acid into our equations: this product of XO is a known antioxidant that can neutralize certain reactivities of superoxide and peroxynitrite (Ames et al., 1981; Kooy et al., 1994). In fact, uric acid and its precursors have been used in protecting against the oxidative neuronal damage in experimental allergic encephalomyelitis, a model of multiple sclerosis,

and, in fact, patients with gout have a markedly reduced likelihood of developing multiple sclerosis (Hooper et al., 1998). Thus, in some pathophysiological conditions, a paradoxical adverse effect of XO inhibition, via reduction of plasma uric acid levels, must also be considered. It is noteworthy that uric acid can actually inhibit XO and thereby act as a feedback inhibitor of the enzyme, although its inhibitory effect was associated with increased superoxide formation (Radi et al., 1992; Tan et al., 1993a). Uric acid can also act as a chelator of iron in extracellular fluids, and this action has been shown to regulate the expression of XO in the lung (Ghio et al., 2002).

From the above data, it appears that one must view XO-derived superoxide generation in the overall complexity of the cellular environment. It is not easy to delineate the relevance of some of these reactions in vivo, but we can assume that some of the above-described interactions and pathways may be relevant in various disease conditions. Overall, it is safe to conclude that inhibition of XO, by reducing superoxide production, is beneficial in most pathophysiological states (see also below). However, the relative contribution of XO-derived superoxide formation (as opposed to other cellular and extracellular sources of superoxide) is unclear and, again, may be dependent on many factors, including the species, the cell type, the tissue, and the type and stage of the particular disease (reviewed in Berry and Hare, 2004; Griendling, 2004; Brandes and Kreuzer, 2005).

IV. Xanthine Oxidase Inhibitors

A. Allopurinol and Oxypurinol

As noted in the Introduction, allopurinol (1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one) (Fig. 3) was initially synthesized as an attempt to produce new antineoplastic agents in the mid-1950s by Falco, but it was found to have inhibitory activity on XO, reducing both urinary and serum uric acid levels [Elion, 1988 (http://nobelprize.org/medicine/laureates/1988/elion-lecture.pdf), 1993]. Allopurinol was approved by Food and Drug Administration in 1966 for treatment of gout and remains a cornerstone in the therapy of primary and secondary hyperuricemia (Rott and Agudelo, 2003;Terkeltaub, 2003;Bieber and Terkeltaub, 2004;Schlesinger, 2004;Pea, 2005;Wortmann, 2005). Allopurinol is rapidly oxidized by XO in vivo to its active metabolite oxypurinol (both isosteres of hypoxanthine and xanthine, respectively), which also inhibits XO. At low concentrations, allopurinol is a substrate for and competitive inhibitor of the enzyme; at higher concentrations, it is a noncompetitive inhibitor. Oxypurinol is a noncompetitive inhibitor of the enzyme; the formation of this compound, together with its long persistence in tissues, is responsible for much of the pharmacological activity of allopurinol.

In terms of pharmacokinetics, allopurinol is rapidly absorbed, reaching peak plasma concentrations within 30 to 60 min, following oral administration. Oxypurinol has lower oral bioavailability than allopurinol. Allopurinol has relatively short half-life in plasma (2–3 h), whereas the half-life of oxypurinol is much longer (14–30 h) due to renal reabsorption (Pea, 2005).

The most common adverse effects of allopurinol are gastrointestinal distress, hypersensitivity reactions, and skin rash. The hypersensitivity reaction may occur even after months or years of medication. These effects generally occur in individuals with decreased renal functions, for whom the dosage of allopurinol was not reduced. Allopurinol may increase the effects of cyclophosphamide and inhibits the metabolism of oral coagulants and probenecid. Symptoms of allopurinol toxicity include fever, rash, vasculitis, eosinophilia, and worsening of renal function, which can lead to a fatal outcome especially in elderly patients with renal insufficiency taking thiazide diuretics (Rott and Agudelo, 2003; Terkeltaub, 2003; Bieber and Terkeltaub, 2004; Schlesinger, 2004; Pea, 2005; see also section V.A.).

By lowering the uric acid concentration in plasma below its limit of solubility, allopurinol facilitates the dissolution of tophi and prevents the development and progression of chronic gouty arthritis (Rott and Agudelo, 2003; Terkeltaub, 2003; Bieber and Terkeltaub, 2004; Schlesinger, 2004; Pea, 2005). The formation of uric acid stones gradually disappears with therapy, and this prevents the development of nephropathy. In addition to the gout and hyperuricemia, there are numerous potential therapeutic applications for allopurinol and oxypurinol in various forms of ischemic and other types of tissue and vascular injuries, inflammatory diseases, and chronic heart failure (see section V. and Tables 1–4).

B. Novel Xanthine Oxidase Inhibitors

Although allopurinol is a very efficient drug, it is a relatively weak XO inhibitor in in vitro assays, with reported IC_{50} values of 0.2 to 50 μM. Ironically, for many contemporary drug discovery programs, this would have probably been well above the threshold numbers for a lead to qualify even for early selection rounds.

The early search for novel XO inhibitors, fueled by the success of allopurinol, focused on synthetic purine and pyrimidine derivatives. However, the drug structural framework based on the purine and pyrimidine motifs is responsible for some side effect caused by allopurinol, i.e., rashes, which are sometimes severe (occurring in 2–8% patients). The rashes result from the metabolic conversion of the drugs to corresponding nucleotides through the action of phosphoribosyl transferase. This prompted a search for new XO inhibitors that are structurally distinct from purines (reviewed in Borges et al., 2002).

A somewhat unexpected but beneficial turn occurred in the 1960s when Fridovich and his colleagues (Hodgson and Fridovich, 1973; McCord and Fridovich, 1968) elucidated the role of XO in free radical production. They later introduced an ingenious assay for generation and detection of superoxide radicals based on the XO/xanthine production of $O_2^{\cdot-}$, inducing chemiluminescence of the lucigenin dye (McCord and Fridovich, 1969). As the quest for medicinal free radical scavengers intensified, this assay was routinely used for screening of the free radical quenching activity of the extracts and natural compounds derived from plants and other sources. Serendipitously, a variety of novel XO inhibitors of varying structures and activity (often low) has been discovered when the validity of the assay was verified. Some known and novel antioxidants and nonantioxidants: phenolic compounds, coumarins, flavonoids, and steroids were found to have relatively high activity and in few instances the initially discovered leads became a subject of more detailed structure/activity studies. Such promiscuity in binding preferences also extends to a wealth of substrates oxidized by XO that includes not only purine derivatives but simple aliphatic, aromatic, and heteroaromatic aldehydes as well (Xia et al., 1999).

During the past decade, definite progress has also been achieved in the understanding of the XO enzyme structure, and rational drug development approaches led to the discovery of new powerful XO inhibitors of various classes, including purine analogs, imidazole and triazole derivatives, and flavonoids among many others (reviewed in Borges et al., 2002). Two of these very potent new compounds, febuxostat [2-[3-cyano-4-(2-methylpropoxy)phenyl)-4-methylthiazole-5-carboxylic acid; TMX-67, TEI-6720] and Y-700 (Fig. 3) are reported to have a favorable toxicology profile, high bioavailability, and more potent and longer-lasting hypouricemic action than allopurinol. These new compounds are currently in human clinical trials for the treatment of hyperuricemia and gout (Okamoto et al., 2003; Yamamoto, 2003; Becker et al., 2004; Fukunari et al., 2004; Hoshide et al., 2004; Komoriya et al., 2004; Yamada et al., 2004; Hashimoto et al., 2005; Mayer et al., 2005; Takano et al., 2005).

Thus, it appears that the hegemony of allopurinol, as a drug in its own league, which essentially had no competitors in clinical use for half a century, is about to change. There are a few structural classes of compounds that are many hundreds times more potent than allopurinol in vitro (both of a purine and nonpurine types). Several drug candidates are either in the development phase or are moving toward clinical testing (Borges et al., 2002; Naito et al., 2000; Okamoto et al., 2003; Nivorozhkin et al., 2003a,b; Yamamoto, 2003; Mabley et al., 2003; Becker et al., 2004; Fukunari et al., 2004; Hoshide et al., 2004; Komoriya et al., 2004; Yamada et al., 2004; Hashimoto et al., 2005; Mayer et al., 2005; Takano et al., 2005). It was clearly established that a xanthine-like structural framework is not a prerequisite for high inhibitory activity. Several recent reports on crystal structure of the different forms of XO, also with bound inhibitors, are indicative of the fact that crystallization techniques have advanced enough to help characterize in the near future protein binding of any lead compound of interest.

V. Therapeutic Areas Relevant for Xanthine Oxidase Inhibitors

A. Xanthine Oxidase Inhibitors in the Treatment of Gout and Tumor Lysis Syndrome

As already mentioned in the previous section, currently, the main indication for XO inhibitors is the treatment of hyperuricemia and gout. Gout is a common disease with prevalence of >2% in men older than 30 years and in woman older than 50 years according to the Third National Health and Nutrition Examination Survey (1988–1994) (Kramer and Curhan, 2002; Choi and Curhan, 2005). The prevalence increases with increasing age, reaching 9% in men and 6% in women older than 80 years (reviewed in Choi and Curhan, 2005). Furthermore, recent epidemiological studies indicate that the overall disease burden of gout is increasing (reviewed in Choi and Curhan, 2005). Indeed, a recent study based on a managed care population in the United States has suggested that the overall prevalence of gout or hyperuricemia increased by 80% from 1990 to 1999 (Wallace et al., 2004).

Gout occurs in individuals who have high serum uric acid levels, in response to precipitation of monosodium urate monohydate crystals in various tissues, followed by an inflammatory response. Typical symptoms of gout include acute recurrent gouty arthritis, a tophinodular collection of monosodium urate crystals and uric acid urolithiasis. The cornerstone of the prevention and treatment of gout is antihyperuricemic therapy, either by uricosuric drugs or by XO inhibitors, such as allopurinol. The area of gout therapy has been reviewed in multiple recent articles (McCarthy et al., 1991; Star and Hochberg, 1993; Terkeltaub, 1993; Davis, 1999; Pal et al., 2000; Pascual, 2000; Rott and Agudelo, 2003; Terkeltaub, 2003; Bieber and Terkeltaub, 2004; Schlesinger 2004; Pea, 2005; Wortmann, 2005), as well as in various textbooks, and is not discussed herein in detail.

An additional, important indication for the clinical use of allopurinol and possibly future XO inhibitors is tumor lysis syndrome associated with tumor chemotherapy (Maurer et al., 1988; Smalley et al., 2000). It is clear that in both indications, XO inhibition is very effective. Allopurinol, which yields its active metabolite oxypurinol in vivo, irreversibly inhibits XO. Although the therapeutic dose of allopurinol is rather high, the administration of a high dose, on its own, would not necessarily represent a problem. The problems and, therefore, the need for new, improved XO inhibitors are mainly related to the relatively high incidence of adverse effects seen with allopurinol in patients with gout. These effects include acute problems (fever and rash), as well as progressively developing leukocytosis, eosinophilia, vasculitis, aseptic meningitis, nephritis and renal dysfunction, and hepatic dysfunction (Jarzobski et al., 1970; Boyer et al., 1977; Wolkenstein and Revuz, 1995; Parra et al., 1995; Duchene et al., 2000; Khoo and Leow, 2000; Greenberg et al., 2001). The so-called “allopurinol hypersensitivity syndrome” can sometimes result in fatal outcome (Arellano and Sacristan, 1993).

The alternatives to allopurinol are rather limited. Therapeutic options in those patients in whom traditional uricosuric drugs are contraindicated, ineffective, or poorly tolerated include slow oral desensitization to allopurinol and cautious administration of oxypurinol. Allopurinol desensitization is useful particularly in those for whom other treatment modalities have failed. If available, benzbromarone may be effective in patients with gout and mild-to-moderate renal insufficiency. Recombinant urate oxidase is not widely available, but it certainly has shown promise for the short-term prophylaxis and treatment of chemotherapy-associated hyperuricemia in patients with lymphoproliferative and myeloproliferative disorders (Fam, 2001).

B. Xanthine Oxidase and Ischemia-Reperfusion Injury

In the early 1980s Granger et al. (1981, 1986) demonstrated that ischemic bowel injury occurred only on reperfusion and was attenuated by superoxide dismutase. On the basis of this observation, the hypothesis was put forward that XO-derived reactive oxygen species (ROS) contribute to the ischemic injury via ATP catabolism during hypoxia and increased electron acceptor availability on reperfusion (Fig. 4). Since the introduction of the concept of ischemia-reperfusion injury (Granger et al., 1981; McCord, 1985), several lines of evidence support the role of XO-derived ROS generation and beneficial effects of XO inhibitors against ischemic damage of the heart, brain, intestine, liver, kidney, lung and other tissues were shown (see below and Tables 1–4).

1. Xanthine Oxidase and Myocardial Ischemia-Reperfusion Injury—One of the longest studied and most controversial research areas in the field of XO is related to the pathogenetic role of XO in myocardial infarction. A detailed analysis of the findings in this experimental model will help illustrate the difficulties and controversies related to investigations into the pathophysiological role of XO.

Studies more than two decade ago reported that the administration of allopurinol has salutary effects on ischemic and reperfused hearts (overviews in McCord, 1985; Schrader, 1985; Berry and Hare 2004) (see also Table 1). For example, Manning et al, (1984; reviewed in Hearse et al., 1986) demonstrated that reperfusion-induced arrhythmias and infarct size are reduced by allopurinol in rats. Similar findings were reported by a variety of other authors using allopurinol or oxypurinol in diverse rat, rabbit, canine, and pig models (Wexler and McMurtry, 1981; Akizuki et al., 1985; Chambers et al., 1985; Stewart et al., 1985; Godin et al., 1986; Myers et al., 1986; Werns et al., 1986; Badylak et al., 1987; Charlat et al., 1987; Godin and Bhimji, 1987; Grum et al., 1987; Brown et al., 1988). At the same time, there were a number of groups that could not confirm the protective effect of allopurinol in various models of myocardial ischemia and reperfusion, especially in response to more severe periods of ischemia (Reimer and Jennings, 1985; Parratt and Wainwright, 1987; overview in Richard et al., 1990).

Relatively early on, the following question arose: Are the effects of allopurinol, indeed, related to the inhibition of XO, or are they related to other pharmacological actions of this agent? Another, related question that arose was the following: Is there XO or an increase in XO in the reperfused heart? With respect to the specificity of allopurinol, Das and colleagues reported in 1987 that both allopurinol and oxypurinol exerted direct free radical scavenging effects in isolated hearts, and exerted cardioprotective effects despite no detectable XO activities in the preparations used (Das et al., 1987; Downey et al., 1987; Hopson et al., 1995). These findings were in stark contrast with other studies demonstrating detectable XO activities in reperfused hearts and its inhibition by allopurinol (Chambers et al., 1985; Brown et al., 1988; Terada et al., 1991; Werns et al., 1991; Ashraf and Samra 1993). From these findings, one conclusion was clear: even if there is XO activity in the reperfused heart and even if allopurinol or oxypurinol is able to inhibit this activity, the additional, nonselective actions of these

compounds [such as free radical scavenging effects as well as other nonspecific effects such as copper chelation (Malkiel et al., 1993), superoxide scavenging (Arai et al., 1998), inhibition of lipid peroxidation (Coghlan et al., 1994; Belboul et al., 2001; Kinugasa et al., 2003) and heat shock factor expression (Nishizawa et al., 1999), Ca^{2+}-sensitizing (Perez et al., 1998), and effects on the antioxidant status of the cells (Qayumi et al., 1993; Yang et al., 1995)] will make the interpretation of the data difficult. Nevertheless, it is now generally accepted that XO is present in the heart (including human heart) (MacGowan et al., 1995; Berry and Hare, 2004), and substrate accumulation does occur during ischemia, which, ultimately, results in the production of free radicals during the reperfusion stage (Xia and Zweier, 1995).

Although the mechanism of action remained questionable (or, in the very least, multiple), follow-up work confirmed the cardioprotective effects of allopurinol and extended them to hypoxic storage and cardioplegia conditions (Bergsland et al., 1987; Vinten-Johansen et al., 1988), cardiopulmonary surgery (Coghlan et al., 1994; Castelli et al., 1995), and acute cardiac allograft rejection (Akizuki et al., 1985).

The cardioprotective effects of allopurinol are clinically exploitable (even if not all of these effects are related to XO inhibition). In a randomized trial conducted in 169 patients, allopurinol significantly decreased early hospital mortality rate after coronary bypass surgery and improved cardiac performance, scored by cardiac index and the need for inotropic or mechanical support (Johnson et al., 1991). In another study (conducted in 90 patients), allopurinol reduced arrhythmias, the need for inotropes, and perioperative myocardial infarction in patients undergoing elective coronary artery bypass grafting (Rashid and William-Olsson, 1991). Allopurinol was also found to reduce lipid peroxidation during coronary artery bypass grafting (50 patients) (Coghlan et al., 1994) and facilitated the recovery of cardiac output and left ventricular stroke work, while reducing plasma uric acid levels in 33 patients (Castelli et al., 1995). In patients with stable angina (60 patients) combination therapy with erinit and allopurinol led to a significant decrease in serum and daily urinary levels of uric acid and lipid peroxidation antioxidative system and an improvement of central hemodynamics (Kaliakin and Mit'kin, 1993). However, in the above referenced Coghlan et al. (1994) study as well as in other small studies by Taggart et al. (1994) (20 patients), Coetzee et al. (1996) (52 patients), no improvements in cardiac function were seen in the patients. Further complicating the picture, in a double-blind, randomized therapy study of 140 patients with ischemic heart disease, allopurinol surprisingly increased the incidence of myocardial infarct extension, suggesting that it may actually be contraindicated in patients with ischemic heart disease (Parmley et al., 1992).

Thus, the data are rather conflicting, with no large-scale multicenter trial data available. Clearly, larger randomized studies are required to determine the ultimate utility of allopurinol in acute myocardial reperfusion conditions.

Although allopurinol's efficacy has not been directly proven, another area in which the agent is widely used in cardioprotection is cold storage: allopurinol is a constituent of the University of Wisconsin (UW) storage solution (Okada et al., 1995; Askenasy and Navon, 1998; Hegge et al., 2001) (see below for more detail).

2. Xanthine Oxidase and Stroke—By the analogy of the cardioprotective effects of allopurinol, the compound has also been tested in various models of ischemic and reperfused brain (Table 2). Allopurinol was found to be protective against mortality and neurological impairment in a stroke model in spontaneously hypertensive rats (Itoh et al., 1986). In a gerbil model of stroke, tungsten-mediated inhibition of XO, but not allopurinol, was shown to protect against neurological deficits (Patt et al., 1988). In a permanent middle cerebral artery occlusion model in Sprague-Dawley rats, allopurinol pretreatment reduced infarct size by approximately

35% (Martz et al., 1989). Similar to allopurinol in a rat model of transient middle cerebral artery occlusion, oxypurinol reduced the ischemic cerebral damage and attenuated the neurological deficits (Lin and Phillis, 1991,1992;Phillis and Lin, 1991). Allopurinol was also effective in a rabbit model of focal cerebral ischemia (Akdemir et al., 2001) and in hypoxic-ischemic injury models in rat pups, as well as in newborn lambs, even if its administration was delayed to the beginning of the reperfusion period (Palmer et al., 1990,1993;Shadid et al., 1998). Allopurinol, at relatively high doses, was also effective in transient middle cerebral occlusion models (Lindsay et al., 1991). In a relatively mild model of stroke (20 min of ischemia and 10–90 min of reperfusion), oxypurinol produced improvements in cellular ATP levels (Phillis et al., 1995). It must also be mentioned that in some studies oxypurinol was without significant protective effects (Arai et al., 1998;Nakashima et al., 1999), and the reasons for these differences between the outcome of these various studies are unclear.

As in the case of myocardial infarction, the multiple potential modes of allopurinol's protective action must always be kept in mind when one interprets the results of the stroke studies. Nevertheless, in vitro studies clearly demonstrate that, at least in rodents, hypoxia and reoxygenation increase the activity of XO and XDH, possibly due to a direct action of excitatory amino acids such as kainate (Battelli et al., 1995, 1998; Sermet et al., 2000). In addition, there is some evidence that the hypoxic and reoxygenation injury to the cerebral vasculature, especially to the endothelial cells, is dependent on XO (Beetsch et al., 1998; Wakatsuki et al., 1999).

So far, the human therapeutic experience with allopurinol is limited to one study conducted in 22 severely asphyxiated infants (Van Bel et al., 1998). In this study, allopurinol tended to improve survival, and exerted beneficial effects on free radical formation, cerebral blood flow volume, and electrical brain activity. Larger follow-up studies are required to expand on these pilot findings.

Interestingly, a recent study has shown increased XO activity being partially responsible for the generation of oxygen free radicals in a rat model of traumatic brain injury, suggesting that inhibition of XO may be of potential therapeutic benefit in neurotrauma (Solaroglu et al., 2005).

3. Xanthine Oxidase and Splanchnic Ischemia-Reperfusion—Allopurinol pretreatment is protective in the ischemic and reperfused gut and beneficially affects the changes in vascular permeability (Parks et al., 1982; Parks and Granger, 1983; Granger et al., 1986; Kulah et al., 2004), neutrophil infiltration (Grisham et al., 1986; Riaz et al., 2002), bacterial translocation (Deitsch et al., 1988; Vaughan et al., 1992), intestinal inflammatory chemokine levels (Riaz et al., 2003), motility (Hakguder et al., 2002), and mortality (Megison et al., 1990). Most of the early studies are reviewed in Schoenberg and Beger (1993). XO-derived superoxide may trigger histamine release in the reperfused gut (Boros et al., 1989). Protection against gut reperfusion injury can also be achieved by inhibition of XO by tungsten (Pitt et al., 1991).

Similar to the situation in the reperfused heart, doubts have been raised with respect to the specificity of allopurinol's action in protecting the ischemic gut (Garcia Garcia et al., 1990; Boros et al., 1991; Nilsson et al., 1994). There are also disagreements with respect to the time course and importance of the conversion of XO to xanthine dehydrogenase during the course of intestinal ischemia (Parks et al., 1988; Vatistas et al., 1998).

Other than reports demonstrating increases in human gut XO activity in response to reperfusion (Wilkins et al., 1993), the clinical experience with respect to XO, allopurinol, and gut is limited

to the use of the allopurinol-containing University of Wisconsin preservation solution during colon surgery (Tesi et al., 1996; Kawashima et al., 1999).

4. Xanthine Oxidase and Ischemia-Reperfusion of Liver, Kidney, Lung, and Other Organs—There is significant experimental evidence on the role of XO in the ischemic and reperfused liver and kidney. In the liver, multiple studies demonstrated both the up-regulation of XO, the conversion of XO to XDH during ischemia (Engerson et al., 1987; McKelvey et al., 1988; Frederiks and Bosch, 1996), as well as the protective effects of allopurinol, tungsten, or BOF-4272 in terms of improved morphology and renal function or hepatic enzyme release during reperfusion (Linas et al., 1990; Saugstad, 1996; Rhoden et al., 2000a,b; Kakita et al., 2002; Yildirim et al., 2002; Willgoss et al., 2003) in most, but not all (Metzger et al., 1988), studies. XO-derived reactive oxygen species have been proposed to act as mediators of inflammatory signal transduction pathways and proinflammatory gene expression (Matsumura et al., 1998; Matsui et al., 2000). An important feature of XO release from the damaged liver is the fact that this enzyme can, in turn, act as a circulating mediator and induce remote organ injury.

Concerning reperfusion injury to the kidney, almost three decades ago, Owens et al. (1974) reported significant protection against kidney transplantation damage by allopurinol. Although the evidence in human kidney preservation and storage was less convincing (Toledo-Pereyra et al., 1977), allopurinol became a standard constituent of the widely used UW organ storage solution. Based on cold ischemic damage studies in rat kidney, allopurinol was, in fact, confirmed as an active ingredient of the UW solution (Biguzas et al., 1990; Gulian et al., 1992; Booster et al., 1994). Interestingly, in a recent study propofol (an anesthetic) attenuated liver ischemia-reperfusion injury in patients undergoing liver surgery by reducing superoxide dismutase and XO activity (Lin et al., 2004).

Allopurinol may also have beneficial effects in ischemic and reperfused kidneys in situ. Hestin and Johns (1999) found that in a rat model of kidney ischemia and reperfusion, allopurinol ameliorated the decrease in kidney hemodynamic and excretory function, at least for the initial few hours of reperfusion. In addition, Rhoden et al. (2000b) demonstrated that allopurinol suppressed the oxidative damage seen in a renal ischemia-reperfusion model in uninephrectomized rats. Pretreatment with allopurinol also improved renal function after repetitive brief ischemia-reperfusion in the isolated perfused rat kidney (Willgoss et al., 2003). In addition to the above-mentioned reports, there is good evidence for the protective effect of XO inhibition against the ischemia-reperfusion injury in the lung (Lynch et al., 1988; Aiba et al., 1992; Okuda et al., 1993) but apparently not in skeletal muscle (Dorion et al., 1993).

C. Xanthine Oxidase and Circulatory Shock

Most of the experimental experience with respect to XO, allopurinol, and circulatory shock is related to hemorrhagic shock models. This is not surprising, as hemorrhagic shock presents many parallels with various forms of ischemia-reperfusion and in fact is considered by many investigators as a form of whole-body ischemia-reperfusion. In the late 1960s and early 1970s Smith and colleagues, Lazarus and colleagues, and other groups demonstrated that allopurinol treatment protects against mortality and organ injury associated with various models of severe hemorrhagic shock (Crowell et al., 1969; Baker, 1972; Lazarus et al., 1974; Hopkins et al., 1975). Allopurinol protected against hepatic damage, reduced the degree of DNA injury, and maintained tissue high energy phosphate levels (Lazarus et al., 1974; Hopkins et al., 1975; Cunningham and Keaveny, 1978). Additional protective modes of allopurinol's action were found to include protection against vascular injury and progressive hemodynamic decompensation (Parks et al., 1983, Allan et al., 1986; Bond et al., 1988; Flynn et al., 1997,

1999) and reduction in intestinal bacterial translocation (Deitch et al., 1988). Similar to the various forms of ischemia-reperfusion injury models (see above), a conversion of XDH to XO has been proposed to occur in hemorrhagic shock. Circulating XO appears to be involved in the generation of remote organ injury associated with hemorrhagic shock (see below).

Some experimental evidence also exists with respect to increased XO expression and limited beneficial effects of allopurinol in other forms of shock (endotoxic, septic, traumatic, anaphylactic, and burn-induced) (Parker and Smith, 1972; Shatney et al., 1980; Saez et al., 1984; McKechnie et al., 1986; Novotny et al., 1988; Lochner et al., 1989; Ahn et al., 1990; Castillo et al., 1991; Ward et al., 1992; Mainous et al., 1993; Xu et al., 1993; Takeyama et al., 1996; Cetinkale et al., 1999; Khadour et al., 2002; Wang et al., 2002).

Unfortunately, the above listed basic observations did not translate into the clinic. According to a recent randomized study by Wijnen et al. (2002), a multiantioxidant supplementation regimen (containing allopurinol, as well as vitamins E and C, mannitol, and *N*-acetylcysteine) failed to affect the changes in gut permeability after lower torso ischemia.

D. Xanthine Oxidase and Chronic Heart Failure

Recent work has indicated a role for XO and XO-related oxidant species in the pathogenesis of chronic heart failure (CHF) (overviews in Landmesser and Drexler, 2002; Berry and Hare, 2004; Doehner and Anker, 2005a; Kittleson and Hare, 2005; Pacher et al., 2005b; Ungvari et al., 2005) (Table 3). In vitro studies in isolated hearts have demonstrated that the progressive development of heart failure is associated with increased myocardial XO levels, which contribute to an enhancement of oxidative stress in the heart (Ferdinandy et al., 1999, 2000). In a heart failure model induced by pacing in the dog, a 4-fold increase in myocardial XO activity or levels was found, with subsequent increases in oxidative stress in the heart (Ekelund et al., 1999; Saavedra et al., 2002; Amado et al., 2005). In a ligation-induced CHF model in the rat, an approximately 50% increase was noted (de Jong et al., 2000). In patients with CHF, elevated circulating uric acid levels have been noted as well as an increase in myocardial XO activity (Leyva et al., 1998; Cappola et al., 2001) (Fig. 5). There was a strong correlation between the levels of uric acid and the severity of chronic inflammation, as evaluated by plasma measurements of soluble intercellular adhesion molecule-1, tumor necrosis factor-α, soluble tumor necrosis factor receptor 2, and E-selectin (Leyva et al., 1998).

The above observations triggered interventional studies with allopurinol. In a study in pacing-induced CHF in the dog, allopurinol induced a decrease in myocardial oxygen consumption and an increase in cardiac contractility and mechanical efficiency at rest (Ekelund et al., 1999) as well as during dobutamine-induced β-adrenergic stimulation and exercise (Ukai et al., 2001). In addition, allopurinol ameliorated increases in afterload and reductions in myocardial contractility during evolving heart failure, thereby preserving ventricular-vascular coupling (Amado et al., 2005). Remarkably, the benefits of allopurinol and ascorbate in dogs with heart failure could be prevented by nitric-oxide synthase (NOS) inhibition, suggesting that XO-derived superoxide may interfere with NO regulation of myocardial energetics (Saavedra et al., 2002). Because XO in failing myocardium is elevated (Ekelund et al., 1999; Ferdinandy et al., 1999, 2000; de Jong et al., 2000; Cappola et al., 2001), the normal interaction between NO and XO may be disrupted in CHF. Interestingly, in a recent study Khan et al. (2004) demonstrated that neuronal NOS (nNOS) and the superoxide-generating enzyme XOR are in physical proximity (coimmunoprecipitate and colocalize) in the sarcoplasmic reticulum of the cardiac myocytes of mice. Deficiency of neuronal NOS but not endothelial NOS was associated with profound increases in XOR-mediated superoxide production, which in turn depressed myocardial excitation-contraction coupling in a manner reversible by XOR inhibition with allopurinol (reviewed in Hare, 2003; Berry and Hare, 2004). These data suggest that nNOS exerts tonic inhibition of XOR-mediated superoxide production that protects the

cardiac myocytes from contractile depression. Therefore, nNOS not only regulates the sarcoplasmic reticulum Ca^{2+} cycle (Khan and Hare, 2003; Khan et al., 2003), but also represents an important antioxidant system, inhibiting XOR activity (Bonaventura and Gow, 2004; Khan et al., 2004). In a recent study by Kögler et al. (2003) oxypurinol boosted the cardiac contractility and improved mechanoenergetic coupling in a rat model of heart failure. Importantly, the inotropic actions of oxypurinol were more pronounced in failing rat myocardium, a tissue that exhibits enhanced XOR activity. Furthermore, oxypurinol did not affect resting tension and intracellular Ca^{2+} transients; thus myocardial function is not impaired (Kögler et al., 2003), which is crucially important from the point of potential therapeutic use of oxypurinol in patients with CHF (Freudenberger et al., 2004). These and similar other preclinical studies have encouraged the clinical testing of oxypurinol for CHF. Despite high hopes for it, allopurinol had no effects on exercise capacity in CHF in 50 patients, although it reduced the B-type natriuretic peptide, an important prognostic marker of CHF (Gavin and Struthers, 2005). After encouraging preliminary results, a phase II multicenter trial evaluating the effects of oxypurinol in 405 patients with CHF failed to show significant benefit in the primary composite endpoints of the study (conducted by Cardioma Pharma Corp.).

In a recent mouse model of heart failure, allopurinol doubled the survival, decreased pathologically elevated XO activity, and improved contractility and response to isoproterenol both in vivo and in isolated cardiac muscle (Stull et al., 2004). Consistent with these results in other recent murine and rat heart failure studies (Engberding et al., 2004; Duncan et al., 2005; Mellin et al., 2005; Minhas et al., 2006; Naumova et al., 2006), investigators have demonstrated reduction of reactive oxygen species production and decreased myocardial dysfunction following allopurinol treatment. Importantly, in addition to the beneficial effect of the drug on left ventricular contractile function, allopurinol treatment also attenuated left ventricular cavity dilation and reduced myocardial hypertrophy and intestinal fibrosis (Engberding et al., 2004; Mellin et al., 2005).

In patients with idiopathic dilated cardiomyopathy, intracoronary administration of allopurinol resulted in an acute, significant improvement in myocardial efficiency by diminishing oxygen consumption in the presence of standard supportive therapy (Cappola et al., 2001). CHF also results in an impairment of peripheral vascular reactivity (possibly via circulating XO, see section V.E. and Table 4). Acute intravenous infusion of allopurinol or chronic treatment with the drug for 1 month improved endothelial function in patients, as evaluated by the measurement of acetylcholine-induced flow responses (Doehner et al., 2002; Farquharson et al., 2002). In a retrospective study in 1760 patients, high-dose treatment with allopurinol was found to beneficially affect survival, whereas low-dose allopurinol treatment actually appeared to increase mortality (Struthers et al., 2002). On the other hand, the degree of autonomic dysfunction was unaffected by allopurinol (Shehab et al., 2001). Long-term prospective evaluation of the possible benefits of allopurinol treatment in CHF is currently lacking.

Considering that the sources of reactive oxygen and nitrogen species in the failing heart are multiple (Sorescu and Griendling, 2002), it is likely that the beneficial effects of inhibition of XO can be enhanced when XO inhibitors are used as part of combination therapy approaches. It must also be kept in mind that some of the effects of allopurinol may be related to free radical scavenging independent of inhibition of XO (as discussed above) and therefore may not always be reproducible with new, more potent XO inhibitors, which may lack allopurinol's additional antioxidant effects. Nevertheless, XO inhibitor therapy in myocardial infarction and chronic heart failure is an appealing possibility for various reasons. First, there is evidence that increased levels of uric acid strongly correlate with mortality rates in congestive heart failure (Fig. 6) (Alderman, 2002; Cicoira et al., 2002; Doehner et al., 2002; Anker et al., 2003; Alderman and Aiyer, 2004), and XO inhibitors exert certain beneficial effects both in animals and humans with heart failure (see Table 3). Second, allopurinol and its active metabolite

oxypurinol are well known and relatively safe drugs that have been used for decades to treat gout. Third, the mechanism of action is unique and thus would be expected to potentiate the beneficial effects of conventional therapeutic agents (e.g., β-blockers and angiotensin-converting enzyme inhibitors).

E. Xanthine Oxidase and Vascular Disease: Hypertension, Hypercholesterolemia, Atherosclerosis, and Diabetes

A substantial body of experimental and epidemiological evidence suggests that serum uric acid is an important, independent risk factor for cardiovascular and renal disease, especially in patients with heart failure, diabetes, and hypertension (overviews in Alderman, 2002; Alderman and Aiyer, 2004; Doehner and Anker 2005b). In patients with coronary artery disease, heart failure, or diabetes, elevated serum uric acid levels are highly predictive of mortality (Fig. 6). Although the mechanisms by which uric acid may play a pathogenetic role in cardiovascular disease are poorly understood, hyperuricemia is associated with deleterious effects on vascular function. It has recently been demonstrated that patients with hyperuricemia had impaired flow-mediated dilation, which was normalized by 3 months of therapy with the XO inhibitor allopurinol (Mercuro et al., 2004). Furthermore, uric acid was found to inhibit both basal and vascular endothelial growth factor-induced nitric oxide production in bovine endothelial cells (Khosla et al., 2005).

Endothelial dysfunction represents a predominant early feature of atherosclerosis, diabetes, hypertension, and heart failure and makes this population prone to cardiovascular complications and microthrombus formation. It has clearly been established that the endothelial dysfunction associated with these disorders is related to the local formation of reactive oxygen and nitrogen species in the vicinity of the vascular endothelium (overview in Li and Shah, 2004). There is accumulating evidence suggesting that XO-derived superoxide significantly contributes to the vascular disease in some of the above-mentioned conditions and the inhibition of XO may exert beneficial effects on impaired vascular function (overview in Berry and Hare, 2004) (see also below and Table 4).

As mentioned in the previous section, there is clinical evidence that allopurinol improves endothelium-dependent vascular function in patients with chronic heart failure (Doehner et al., 2002; Farquharson et al., 2002), in whom endothelium-bound xanthine oxidase activity is increased and inversely correlates with the endothelium-dependent vasodilation (Landmesser and Drexler, 2002). XO inhibition with allopurinol also reverses NO-dependent endothelial dysfunction in heavy smokers (Guthikonda et al., 2003, 2004). Interestingly, tobacco smoke condensate up-regulates XO and increases its activity in pulmonary endothelial cells (Kayyali et al., 2003).

XO has also been implicated in the pathogenesis of endothelial dysfunction associated with hypercholesterolemia and atherosclerosis. Oscillatory shear stress, which occurs at sites of the circulation that are vulnerable to atherosclerosis-induced superoxide production in endothelial cells, was reported to depend on XO activity (McNally et al., 2003). In the vasculature of hypercholesterolemic rabbits, oxypurinol treatment resulted in a decrease in vascular free radical production (Ohara et al., 1993; Mugge et al., 1994; White et al., 1996). XO activity in the vasculature is due to the deposition of circulating XO to sulfated glucosaminoglycans in the intimal surface (White et al., 1996). The original source of the circulating XO in hypercholesterolemia is unclear at present. Also in patients, oxypurinol treatment was found to improve the endothelium-dependent vasorelaxant responses in some (Cardillo et al., 1997) but not other (O'Driscoll et al., 1999) studies. As native and minimally oxidized low-density lipoprotein increases allopurinol-inhibitable superoxide generation in isolated vascular rings, there may be an additional role for local up-regulation of vascular (endothelial) XO levels (Stepp et al., 2002), although the findings may equally be interpretable through the direct

oxidant scavenging effect of allopurinol. Interestingly, the local concentration of uric acid is elevated in atherosclerotic plaques from carotid endarterectomy specimens and XO and cholesterol are colocalized (Patetsios et al., 2001).

There is some recent evidence for the role of XO in the pathogenesis of vascular dysfunction associated with diabetes: there is an elevation in the plasma and liver XO levels in type I diabetic patients (Desco et al., 2002). In aortae from alloxan-induced diabetic rabbits, endothelial superoxide formation is increased and can be blocked by the XO inhibitor allopurinol (Desco et al., 2002). Heparin, which releases bound XO from the endothelial cells, also decreases superoxide production by aortic rings from diabetic rabbits (Desco et al., 2002). Diabetes also causes an increase of XO activity in the liver of rats, and XO is released from the liver of these animals (Desco et al., 2002). Plasma XO activity is therefore increased in diabetic mice and correlated with the degree of superoxide generation 2 weeks after the onset of diabetes and could be normalized by pretreatment with allopurinol or oxypurinol (Matsumoto et al., 2003). In type I diabetic patients allopurinol reduced the degree of oxidative stress (hemoglobin glycation, glutathione oxidation, and lipid peroxidation) (Desco et al., 2002) whereas in type II diabetic patients with mild hypertension, prolonged treatment with allopurinol resulted in significant improvements in peripheral endothelium-dependent vasorelaxant function (Butler et al., 2000). Collectively, it appears that XO plays an important role in the generation of free radicals in diabetes. Given the importance of oxidative stress in the development of diabetic complications XO inhibitors could be of significant therapeutic benefit in diabetic patients.

There is also evidence implicating XO in the pathogenesis of hypertension. In the hearts of hypertensive rats, Janssen et al. (1993) reported increased XO activities. Suzuki et al. (1998) reported increased XO activities in the mesenteric tissues of spontaneously hypertensive rats (SHRs) and normalization of endothelial function and blood pressure in these animals after inhibition of XO activity by tungsten. A tungsten-rich diet also successfully lowered blood pressure in Dahl salt-sensitive hypertensive rats but had no effect on Dahl salt-resistant rats, indicating a potential role for XO-generated ROS in salt-induced hypertension (Swei et al., 1999). Oxypurinol was also shown to lower blood pressure in SHRs but not in controls (Nakazono et al., 1991). Similarly, the mean blood pressure in a dexamethasone-induced hypertension model was also reduced by allopurinol. Furthermore, allopurinol reduced the increased XO level in cremaster muscle of dexamethasone-treated rats but not in controls (Wallwork et al., 2003). In other studies Laakso et al. (1998; 2004) demonstrated that regardless of sodium intake, renal XO activity increased 2-fold during growth in SHRs, but not in Wistar-Kyoto rats. Furthermore renal XO activity correlated with systolic blood pressure in SHRs. Allopurinol exerted negligible effects on blood pressure but prevented hypertension-induced left ventricular and renal hypertrophy in SHRs (Laakso et al., 1998, 2004).

Preincubation with oxypurinol improved the endothelium-dependent vascular relaxation in transgenic rats with elevated angiotensin II levels (Mervaala et al., 2001) and also improved the flow-mediated vascular responses in hyperhomocysteinemic rats (Bagi et al., 2002). There is evidence that elevated uric acid levels correlate with the increase in blood pressure in rats (Mazzali et al., 2001). Furthermore, elevated serum uric acid levels are associated with increased cardiovascular risk in hypertensive patients (Alderman, 1999; Alderman et al., 1999).

In mild gestational hypertension, an indirect measure of XO was increased (Nemeth et al., 2002), and in mild hypertension associated with type II diabetes, chronic treatment with allopurinol improved peripheral vascular function (Butler et al., 2000). However, in another study, endothelium-dependent relaxations of hypertensive patients were unaffected by acute oxypurinol treatment (Cardillo et al., 1997). Thus, either there appears to be no major role for

XO in the pathogenesis of vascular injury in hypertensive (nondiabetic) humans or the endothelial dysfunction that develops is XO-dependent but irreversible.

Although physiological aging is known to be associated with increased oxidative stress in the vasculature (van der Loo et al., 2000; Pacher et al., 2002b; Csiszar et al., 2002), increased XO does not appear to play a major role in the elevated oxidative stress (Csiszar et al., 2002). Interestingly, a recent study has shown that in cultured vascular smooth muscle cells XO is capable of activating promatrix metalloproteinase-2 through non-free radical-dependent mechanisms (Liu et al., 2004).

In conclusion, the above data suggest that XO may play an important role in various forms of vascular dysfunction and injury, and pharmacological inhibitors of the enzyme may represent important new additions to the therapeutic arsenal to treat these conditions, if proven in larger scale clinical trials.

F. Xanthine Oxidase and Inflammatory Bowel Disease and Other Inflammatory Diseases

There is significant evidence for the pathogenetic role of XO in some (Keshavarzian et al., 1990; Siems et al., 1992; Ben-Hamida et al., 1998) but not all (Clark et al., 1988) murine experimental models of colitis and inflammatory bowel disease and duodenal ulceration. Allopurinol has been shown to be an effective addition to standard 5-aminosalicylic acid therapy in human trials (Salim, 1992; Jarnerot et al., 2000). However, in one study, the increased chemiluminescence seen in the colonic mucosa patients with colitis was not inhibitable by allopurinol coincubation in vitro (Sedghi et al., 1993), whereas in another study, no increases in colonic XO activity were demonstrated in human colonic samples (Reynolds et al., 1996). It is possible that basal levels of XO (when converted from XDH), in the presence of other sources of oxidative and nitrosative stress in colitis, contribute to the development of the disease, even in the absence of a clear up-regulation of XO in patients. Alternatively, it is also possible that the beneficial effects of allopurinol in colitis are unrelated to XO inhibition and are actually related to oxyradical scavenging. The latter proposal may be supported by an experimental study by Keshavarzian and colleagues (1990), in which XO depletion with tungsten was ineffective in reducing the symptoms of experimental colitis in rats, whereas allopurinol was effective in the same model. The novel nonpurine XO inhibitor AN-01-24, however, was effective in a murine model of dextran sulfate-induced colitis (Nivorozhkin et al., 2003a).

There is evidence for increased circulating levels of XO in human plasma samples from patients with rheumatoid arthritis (Miesel and Zuber, 1993). Allopurinol ameliorates the symptoms of arthritis in animal models of rheumatoid arthritis (Miesel et al., 1994; Yossif et al., 1995); at least some of these effects are likely related to the antioxidant actions of the compound. (The above referenced models of arthritis do not involve uric acid deposition into the joints. Obviously, by the prevention of hyperuricemia and urate crystal deposition, allopurinol and other XO inhibitors will have a clear and pronounced effect in preventing the development of gouty arthritis, as demonstrated in human clinical practice.)

There is also some evidence for the role of XO in the pathogenesis of sickle cell disease, a disease with a variety of components including inflammation, ischemia-reperfusion, and also a high incidence of hyperuricemia and gout (Reynolds, 1983). There is a significant degree of conversion of XDH to XO and release of XO into the systemic circulation (Osarogiagbon et al., 2000; Aslan et al., 2001). As discussed above, this increased circulating XO activity deposits at the vascular intima and leads to the development of endothelial dysfunction via the local formation of peroxynitrite in the vicinity of endothelial cells (Aslan et al., 2001). Allopurinol also appears to reduce the oxidative stress in sickle cell erythrocytes and in a murine

model of sickle cell disease via a direct scavenging mechanism (Sertac et al., 1997; Osarogiagbon et al., 2000).

Additional inflammatory diseases in which XO has been implicated or the beneficial effect of XO inhibitors have been reported, include pneumonia (Akaike et al., 1990; Ikeda et al., 1992; Miyakawa et al., 2002; Wright et al., 2004), acute respiratory distress syndrome (Mabley et al., 2003), chronic obstructive pulmonary disease (Komaki et al., 2005), nephritis (Roberts et al., 1990; Gwinner et al., 1999), pancreatitis (Niederau et al., 1992; Czako et al., 2000; Folch et al., 2001; Zeki et al., 2002), peritonitis and peritoneal adhesions (Rijhwani et al., 1995; Cavallari et al., 2000), uveitis (Augustin et al., 1994, 1999) and dermatitis (Deliconstantinos et al., 1996). It must be kept in mind, however, that efficacy of allopurinol does not necessarily mean that XO activation is involved. For example, in a study by Augustin et al. (1994) in uveitis, a dose of allopurinol that was effective in blocking XO activity failed to affect the course of the disease, whereas higher doses of the compound (at which antioxidant effects become more prominent) proved effective in reducing the inflammation. The attempts to use allopurinol for anti-inflammatory purposes at the bedside have also failed so far: in a 300-patient study on pancreatitis developing as a complication of endoscopic retrograde cholangiopancreatography, allopurinol was found to be clinically ineffective (Budzynska et al., 2001).

There is some evidence that XO-derived reactive oxygen species play a role in antimicrobial defense (reviewed in Vorbach et al., 2003; Martin et al., 2004). Allopurinol and AHPP each exacerbated mortality in a *Salmonella typhimurium* model of infection in mice (Umezawa et al., 1997). In the absence of functional NADPH oxidase, the allopurinol-related impairment of antibacterial defense was prominent (Segal et al., 2000). Allopurinol has also been shown to increase ear swelling and mortality in a contact hypersensitivity model (Horiuchi et al., 1999a). It is noteworthy that the clinical use of allopurinol is normally not associated with reduced antibacterial defense, although it is possible that this issue has not been systematically investigated. On the other hand, the effects on contact hypersensitivity seen in the murine model do correlate with the clinical experience (hypersensitivity reactions to allopurinol in a significant fraction of the patients).

G. Xanthine Oxidase and Various Forms of Toxic Organ Injury

XO has been implicated and allopurinol treatment has demonstrated effectiveness in a variety of toxic organ injury models. These models include various forms of liver injury, i.e., ones induced by ionizing radiation (Srivastava and Kale, 1999; Srivastava et al., 2002), ethanol (Oei et al., 1982; Lieber, 1997; Kono et al., 2000; Zima et al., 2001), cocaine (Aoki et al., 1997), thioacetamide (Ali et al., 2001), acetaminophen (Knight et al., 2001), and aluminum (Moumen et al., 2001). In the case of ethanol, aluminum, and radiation, enhancement of hepatic XO levels and/or spillage of XO into the circulation were detected (Oei et al., 1982; Zima et al., 1993; Moumen et al., 2001; Srivastava et al., 2002). In the case of paracetamol, it is interesting to note that XO actually participates in the metabolism of the drug, with the generation of toxic by-products (Van Steveninck et al., 1989). Similar oxidant-yielding reductive activation by XO and XDH has been also reported in the case of doxorubicin, streptonigrin, and menadione (Yee and Pritsos, 1997). It is noteworthy that in the acetaminophen hepatotoxicity model, lower doses of allopurinol (sufficient to block XO activity) failed to show protection, whereas higher (antioxidant) levels were effective, indicating that the mode of allopurinol's action is its antioxidant nature in this particular study (Knight et al., 2001). In many other investigations, low and high doses of allopurinol were not compared, but the doses of the compound used were generally sufficient to produce significant antioxidant effects. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine- and manganese-induced neurotoxicity (Miele et al., 1995; Desole et al., 1996; Obata et al., 2001), cisplatin-induced

ototoxicity and nephrotoxicity (Lynch et al., 2005), paraquat-and nitrofurantoin-induced lung injury (Kitazawa et al., 1991; Bernard et al., 1997), and renal contrast nephropathy (Katholi et al., 1998) have also been suppressed by allopurinol in murine and rat studies.

VI. Future Development of Xanthine Oxidase Inhibitors

From the small number of current examples of the development of novel XO inhibitor compounds that have entered a clinical phase (Becker et al., 2004, 2005; Fukunari et al., 2004; Komoriya et al., 2004; Yamada et al., 2004; Hashimoto et al., 2005; Mayer et al., 2005; Takano et al., 2005), it appears that hyperuricemia and gout remain the main indications for the development of novel XO inhibitors, with additional growing interest in cardiac indications, such as chronic heart failure. Novel XO inhibitors must preferably be more potent, more effective, and possess better pharmacodynamic profile than allopurinol/oxypurinol, which is expected to translate in the clinical practice to lower daily doses and/or less frequent daily administration of the drug. Considering current tools for small molecule design and development, achievement of such goals does not appear to be too ambitious, although one must note that oxypurinol, as an irreversible inhibitor of XO, may have advantages over novel, ultrapotent competitive inhibitors of XO. The irreversible inhibition of XO by oxypurinol, in fact, can result in situations, in which new XO inhibitors, that appear to be several orders of magnitude more potent that allopurinol in vitro lose much of their potency advantage over allopurinol in vivo (Horiuchi et al., 1999b,c; Naito et al., 2000; Ishibuchi et al., 2001).

It is important to note that XO inhibitors, including allopurinol, although inhibiting the activity of the enzyme, can actually reduce the enzyme by transfer of an electron to oxygen, thus generating superoxide (Miyamoto et al., 1996). Other XO inhibitors, such as AHPP, do not share this oxidant-generating ability of allopurinol. Although it is unclear whether this finding is relevant for in vivo situations, it is probably preferable to develop future XO inhibitors that do not exert pro-oxidant effects.

A more important area in which XO inhibitors clearly need improvement is the reduction of their side effects. As reviewed above, allopurinol does have a number of serious side effects, and the cellular and molecular mechanisms of these side effects are incompletely understood. Some recent data indicate that the renal toxicity of allopurinol is related to impairment of pyrimidine metabolism (Horiuchi et al., 2000). There are no reliable or rapid screening tools that would predict the safety profile of novel XO inhibitors in terms of hypersensitivity reactions or organ toxicity; contact hypersensitivity mouse ear models and toxicity studies in rodents are being used to predict such side effects (Horiuchi et al., 1999a). Intuitively, one would predict that novel XO inhibitors that would move away from the purine-based inhibitor structure may have fewer of the allopurinol-like side effects (of course, they may introduce new types of side effects or toxicities). One must also be cautious with widely used long-term safety trials, especially in rodents, as rodents and primates have different biochemical pathways for handling purines: urate oxidase is an essential enzyme in rodents that converts uric acid into allantoin, which subsequently metabolizes to allantoate and then glioxylate and urea (Wu et al., 1994).

With respect to the utility of novel XO inhibitors for the experimental therapy of pathophysiological conditions other than gout (reperfusion, inflammation, and toxic organ injury), the first three interrelated questions to be addressed are the following: 1) Is there up-regulation of XO in human disease? 2) Does oxidant generation from XO substantially contribute to the pathogenesis of the disease? and 3) How much of the previously reported effects of allopurinol are actually related to XO inhibition, as opposed to non-XO related additional pharmacological effects of the compound? These issues have been reviewed, in some detail, in the preceding section. For questions 1 and 2, it appears that in many

pathophysiological conditions, there is an up-regulation of XO in humans sometimes coupled with a deposition of circulating XO to the vasculature (as reviewed above). Under these conditions, it does make sense to counteract with the XO-derived oxidant generation. Whether or not XO represents the major source of oxidants in various pathophysiological conditions, as opposed to one of many sources, would determine the right approach to be taken (i.e., XO inhibition versus a more broadly based antioxidant strategy). With respect to question 3, the answer is unknown. In some studies, in which a dose-response relationship with allopurinol has been carefully investigated (as in uveitis and in some forms of toxic liver injury), low doses of allopurinol, which would be expected to inhibit XO, failed to affect the pathogenesis of the disease, whereas high doses become effective (Augustin et al., 1994, Knight et al., 2001). In some other models of disease (stroke and colitis), depletion of XO with tungsten was compared with allopurinol, and, frequently, allopurinol but not tungsten was found to be effective (Patt et al., 1988; Keshavarzan et al., 1990). Based on these studies, one can conclude that non-XO-related actions of allopurinol can be responsible for at least some of (or possibly much of?) the protective effects in disease models. If, indeed, this latter possibility proves to be the case, it would not invalidate the clinical efficacy of allopurinol or oxypurinol in various pathophysiological conditions. Indeed, there are some indications that allopurinol is effective in some forms of human disease (such as CHF, myocardial infarction, and also possibly in inflammatory bowel disease); after all, what ultimately and clinically matters is that the outcome of the disease improves in the patients, regardless of the precise mode of action. Nevertheless, pilot (phase II type) studies need to be confirmed with large phase III type trials. Because allopurinol and oxypurinol are not protected by particularly strong intellectual property positions (although use patents exist, for example, the use of oxypurinol to treat patients with heart failure) and these compounds are not protected by structure-of-the-matter patents and can be made relatively cheaply and simply, it is unlikely that large pharmaceutical firms would be interested in sponsoring such phase III trials. Nevertheless, qualified investigators, in collaboration with granting agencies, nonprofit foundations, or government bodies may be able to organize such testing. At any rate, it is unclear whether the development of allopurinol for its antioxidant properties would be competitive compared with the development of so-called catalytic antioxidant molecules (e.g., low-molecule superoxide dismutase mimics or peroxynitrite decomposition catalysts), which are likely to be substantially more effective than allopurinol in neutralizing oxidants in the same disease conditions, as they would interfere with oxidants derived not only from XO, but also from a variety of other sources (mitochondria, NADPH oxidase, nitric-oxide synthase, etc.).

As with most preclinical studies, it also remains to be determined whether preclinical data observed in somewhat artificial animal models of disease are actually applicable to the human condition, especially in light of the differences between the XDH/XO systems in primates versus lower species. It is noteworthy that, so far, practically all published efficacy data associated with the novel XO inhibitor compounds relate to the area of gout, and researchers have not tested or reported efficacy of these compounds in preclinical models of inflammation or reperfusion or toxic organ injury (Okamoto et al., 2003; Yamamoto, 2003; Becker et al., 2004; Fukunari et al., 2004; Hoshide et al., 2004; Komoriya et al., 2004; Yamada et al., 2004; Hashimoto et al., 2005; Mayer et al., 2005; Takano et al., 2005). The XO inhibitor pterin-6-aldehyde is a known superoxide scavenger (Mori et al., 1998) and probably so are the 2-alkyloxyalkylthiohypoxanthines as well (Biagi et al., 2001). BOF-4272 and AHPP appear to reduce oxidative stress in the liver and lung in vivo (Matsumura et al., 1998; Miyakawa et al., 2002). There are only a few reports to investigate whether or not the other classes of novel XO inhibitor compounds share some of the antioxidant or non-XO-related activities of allopurinol. Even if they do have such effects, one would expect that the therapeutic dose of the novel, more potent XO inhibitors would be much lower than that of allopurinol. Thus, antioxidant effects would be expected to contribute less to the in vivo actions of the new XO inhibitors.

Taken together, allopurinol remains the cornerstone of current clinical management of hyperuricemia and gout, despite its problematic side effect profile. There is room for the development of novel XO inhibitors for the experimental therapy of hyperuricemia and gout, which are major medical indications and major drug markets worldwide. It is currently unclear whether novel XO inhibitors will be effective (and/or competitive with other antioxidant approaches) for the experimental therapy of ischemic conditions, inflammatory diseases, CHF, and various forms of organ injury. Several series of novel XO inhibitors have entered clinical testing, and, undoubtedly, there is interest for the development of additional, novel series of XO inhibitors. It will be interesting to see how the efficacy and safety profiles of these novel agents compare to those of allopurinol.

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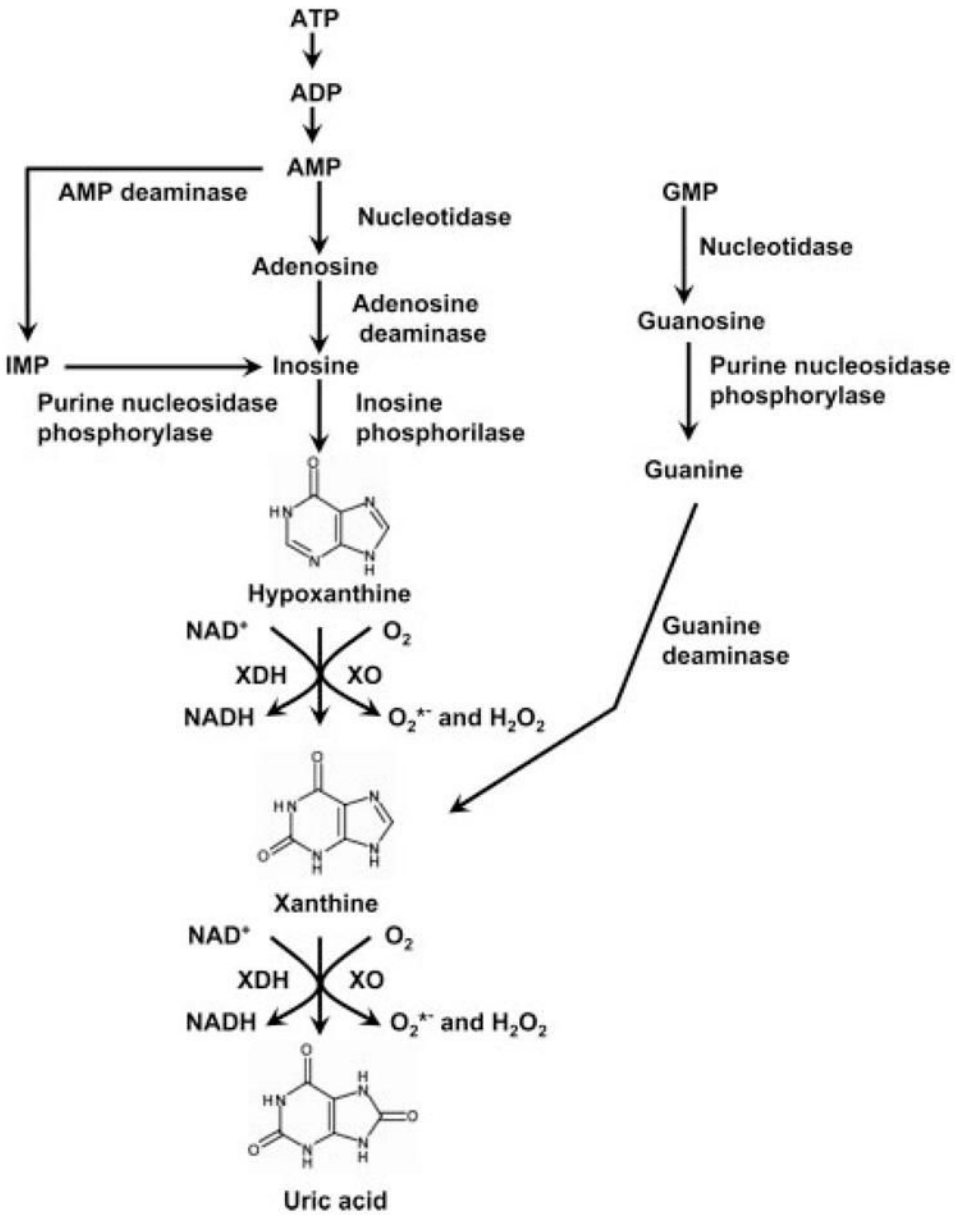

Fig. 1.
Schematic diagram of the purine degradation pathway.

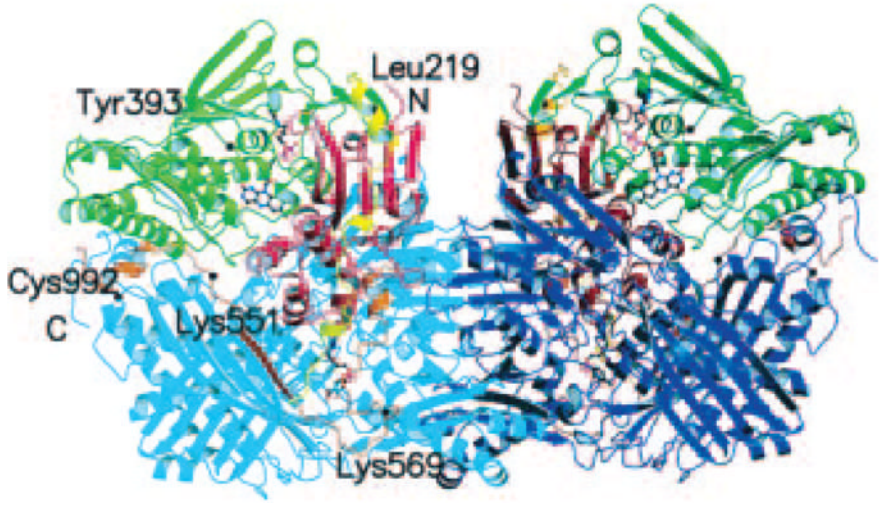

Fig. 2.

Crystal structure of the xanthine dehydrogenase dimer divided into the three major domains and two connecting loops. The two monomers have symmetry related domains in the same colors, in lighter shades for the monomer on the left and in darker shades for the monomer on the right. From the N to the C terminus, the domains are the iron/sulfur-center domain (residues 3–165; red), the FAD domain (residues 226–531; green), and the molybdopterin center (Mo-pt) domain (residues 590–1331; blue). The loop connecting the iron/sulfur domain with the FAD domain (residues 192–225) is shown in yellow, the one connecting the FAD domain with the Mo-pt domain (residues 537–589) is in brown, and the N and C termini are labeled. The FAD cofactor, the two iron/sulfur centers, the molybdopterin cofactor, and the salicylate also are included (Enroth et al., 2000).

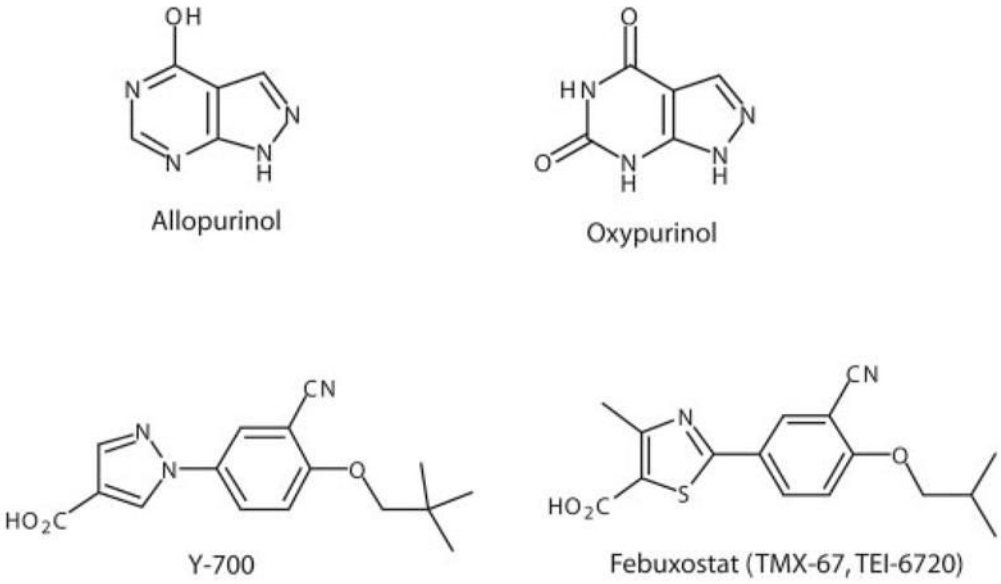

Fig. 3.
Chemical structures of selected xanthine oxidase inhibitors.

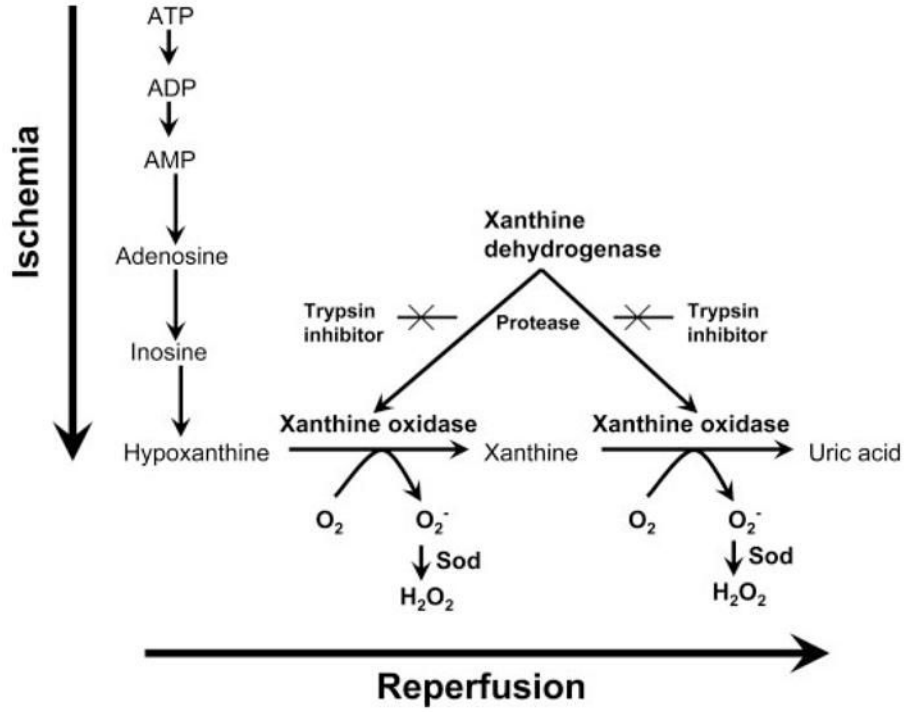

Fig. 4.

Ischemia-reperfusion injury hypothesis. During the course of ischemia, transmembrane ion gradients are dissipated, allowing cytosolic concentrations of calcium to rise, which in turn, activates protease that irreversibly converts XDH, predominant in vivo, into XO. At the same time, cellular ATP is catabolized to hypoxanthine, which accumulates. During the reperfusion, XO using readmitted oxygen and hypoxanthine generates superoxide and hydrogen peroxide. Scheme derived from Granger et al. (1981, 1986) and McCord (1985).

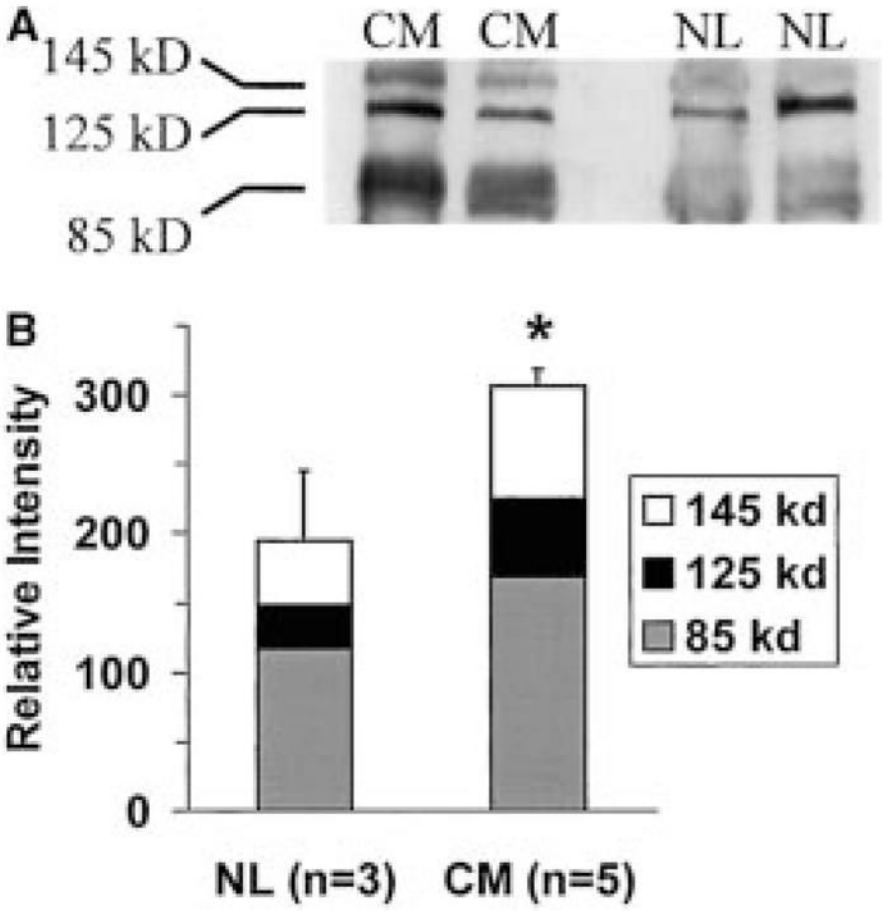

Fig. 5.

XOR is up-regulated in patients with heart failure. A, representative Western blot of myocardial extracts from patients with end-stage idiopathic dilated cardiomyopathy (CM) and patients with normal cardiac function (NL) probed with monoclonal anti-XDH antibody. Bands corresponding to both XDH (145 kDa) and XO (125 and 85 kDa). B, densitometry depicting the average XDH/XO signal from all patients. The total XDH/XO signal is increased by 60% in idiopathic dilated cardiomyopathy. *, $P < 0.05$ by Student's unpaired *t* test. Reprinted from Cappola et al. (2001), with permission from Lippincott Williams & Wilkins (Philadelphia, PA).

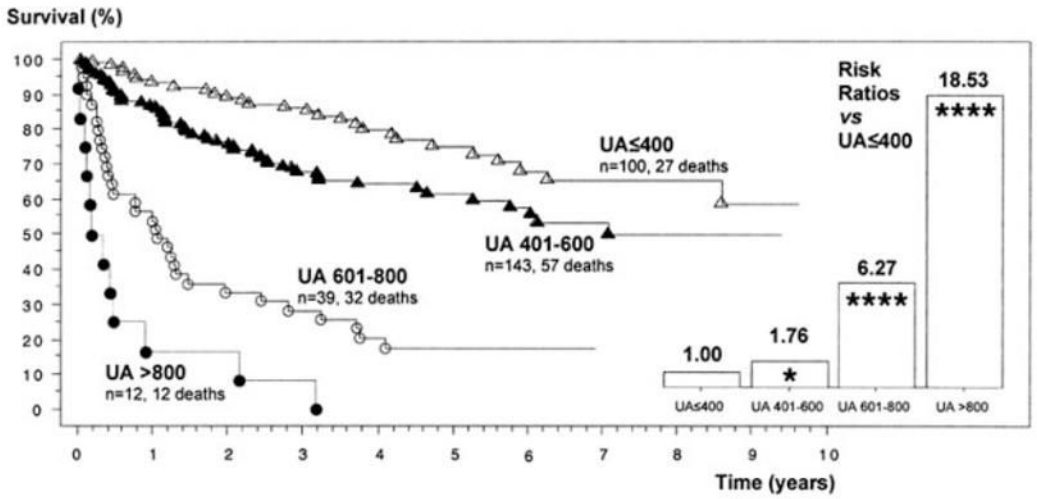

Fig. 6.

Serum uric acid (UA) levels and survival in CHF patients. A recent study in 294 chronic heart failure patients indicates a graded relationship between serum uric acid levels and survival. The plots show Kaplan-Meier survival curves and hazard ratios for different serum uric acid levels. Patients with normal UA (400 μM) had best survival (at 12 months, 93%) compared with patients with UA between 401 and 600 μM [87%, risk ratio [RR] 1.76 (1.11 to 2.78)], patients with UA between 601 and 800 μM [RR 6.27 (3.73 to 10.54)], and patients with UA >800 μM [17%, RR 18.53 (9.18 to 37.42)]. Reprinted from Anker et al. (2003), with permission from Lippincott William & Wilkins.

TABLE 1

Effects of XO inhibitors in myocardial ischemia-reperfusion injury

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
Rat	Myocardial infarction-induced by isoproterenol	Allopurinol	Reduced myocardial damage	Wexler and McMurthy (1981)
Rat	Myocardial I/R	Allopurinol	Decreased reperfusion-induced arrhythmias	Manning et al. (1984)
Rat heart	Myocardial I/R	Oxypurinol	Reduction of myocardial damage and decrease of myocardial vascular resistance	Badylak et al. (1987)
Rat heart	Hypothermic cardioplegia, myocardial I/R	Allopurinol	Improved cardiac function	Bergsland et al. (1987)
Rat	Myocardial I/R	Allopurinol	Reduction of myocardial infarct size	Montor et al. (1987)
Rat/rabbit heart	Myocardial I	Allopurinol	Improved postischemic function in rats but not in rabbits	Grum et al. (1987)
Rat heart	Myocardial I/R	Allopurinol	Improved function during reperfusion and higher ATP levels	Lasley et al. (1988)
Rat heart	Myocardial I/R	Allopurinol	Better ventricular function after I/R	Brown et al. (1988)
Rat heart	Myocardial I/R	Allopurinol	Better recovery of ventricular function and decreased incidence and duration of reperfusion-induced arrhythmias without effects on recovery of ATP, creatine and inorganic phosphates, and H^+	Headrick et al. (1990)
Rat	Myocardial I	Allopurinol	No effect on the infarct size and failure to improve cardiac function	Boucher and de Leiris (1991)*
Rat heart	Myocardial I/R	Allopurinol	Improved postischemic recovery of cardiac function, but this result is attributed to an unrelated effect to XO inhibition	Chambers et al. (1992)
Rat heart	Myocardial I/R	Allopurinol	Increased XO activity during I/R in interstitial cells, coronary vessel endothelium, and smooth muscle cells detected by immunocytochemistry, which was reduced by allopurinol	Ashraf and Samra (1993)
Rat heart	Myocardial I/R	Allopurinol	Intermittent infusion of allopurinol during global myocardial ischemia resulted in improved myocardial functional recovery and improved preservation of high-energy phosphates	Sakakibara (1993)
Rat heart	Myocardial I/R	Allopurinol	Reduced the incidence and severity of reperfusion arrhythmias and increased the tissue ascorbate levels	Yang et al. (1995)
Rat heart, right ventricular trabeculae	Myocardial I/R	Allopurinol, Oxypurinol	Ca^{2+}-sensitizing effect of allopurinol and oxypurinol underlying the preservation of contractility in a model of stunned myocardium	Perez et al. (1998)
Rat heart	Myocardial I/R	Allopurinol	Reduced accumulation of mRNA for heat shock proteins (HSP70 and HSP90) after repetitive ischemia/reperfusion	Nishizawa et al. (1999)
Rat heart	Myocardial I/R	Allopurinol	Allopurinol significantly inhibited myocardial xanthine oxidase activity, improved left ventricular dysfunction after ischemia, and decreased myocardial lipid peroxidation and superoxide formation	King et al (1998)*
Guinea pig isolated right ventricular segment	Myocardial I/R	Allopurinol	Reduced the incidence and severity of reperfusion arrhythmias	Li and Ferrier (1992)

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
Rabbit	Myocardial I/R	Allopurinol	Decreased reperfusion-induced arrhythmias and protected against ultrastructural damage	Godin et al. (1986)
Rabbit	Myocardial I/R	Allopurinol	Protection of the I/R myocardium to t- butylhydroperoxide induced glutathione depletion and production of thiobarbituric acid reactive substances, which was not associated with any significant alterations in tissue ATP levels or in the activities of the myocardial antioxidant enzymes catalase, Cu,Zn-superoxide dismutase, or glutathione peroxidase, suggesting that allopurinol may exert its effects by direct radical scavenging or by some other mechanism unrelated to xanthine oxidase inhibition.	Godin and Garnett (1989)
Rabbit	Myocardial I/R	Allopurinol	Better preservation of cellular ATP levels and mitochondrial ATP generation during ischemia and prevention of the decrease in left ventricular pressure, sodium and calcium accumulation, and decreases in sarcolemmal Na^+,K^+-stimulated and sarcoplasmic reticulum K^+,Ca^{2+}-stimulated ATPase activities	Godin and Bhimji (1987)
Rabbit heart	Hypothermic cardioplegia, myocardial I/R	Allopurinol	Improved cardiac function	Myers et al. (1986)
Rabbit heart	Myocardial I/R	Allopurinol	No detectable XO activity and reduction of the infarct size	Downey et al. (1987)*
Rabbit heart	Myocardial I/R	Allopurinol	Decreased XO activity and improved ventricular developed pressure, peak systolic pressure, and coronary flow	Terada et al. (1991)
Dog	Myocardial I	Allopurinol	No reduction of the infarct size	Shatney et al. (1976)*
Dog	Myocardial I/R	Allopurinol	Reduction of infarct size	Chambers et al. (1985)
Dog	Myocardial I	Allopurinol	Reduction of infarct size	Akizuki et al. (1985)
Dog	Myocardial I/R	Allopurinol	No reduction of the infarct size	Reimer and Jennings (1985)*
Dog	Hypothermic cardioplegia, myocardial I/R	Allopurinol	Improved left ventricular function	Stewart et al. (1985)
Dog	Myocardial I/R	Allopurinol	Reduction of infarct size	Werns et al. (1986)
Dog	Myocardial I/R	Allopurinol	Better recovery of systolic contractile function following reperfusion	Charlat et al. (1987)
Dog	Myocardial I/R	Allopurinol	No decrease in I/R-induced arrhythmias	Parratt and Wainwright, (1987)*
Dog	Myocardial I	Allopurinol	Reduction of infarct size	Kingma et al. (1987, 1989)
Dog	Myocardial I/R	Oxypurinol	Improved regional ventricular function after reperfusion, but failed to reduce infarct size	Puett et al. (1987)
Dog	Myocardial I	Allopurinol	Delayed but did not prevent infarction in the permanent occlusion model	Miura et al. (1988)
Dog	Myocardial I/R	Oxypurinol	No reduction of the infarct size	Kinsman et al. (1988)*
Dog	Myocardial I	Allopurinol	No reduction of the infarct size if allopurinol was given 1 min postocclusion	Kingma et al. (1988)*
Dog	Myocardial I/R	Allopurinol, Oxypurinol	Oxypurinol but not allopurinol given before reperfusion reduced	Matsuki et al. (1990)

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
			the infarct size but not ventricular arrhythmias	
Dog	Myocardial I/R	Oxypurinol, Amflutizole	Xanthine oxidase inhibition was demonstrated in each of the drug treatment groups, but only oxypurinol limited the extent of myocardial injury	Werns et al. (1991)
Dog	Myocardial I/R	Allopurinol	Reduction of infarct size	Motoe and Yoshida (1991)
Dog	Myocardial I/R	Allopurinol	Improved endothelium-dependent coronary vascular relaxation in vitro	Sobey et al. (1992)
Dog	Myocardial I/R	Allopurinol	Improved contractility, decreased lipid peroxidation	Konya et al. (1993)
Dog	Myocardial I/R	Allopurinol	Improved endothelium-dependent coronary vascular relaxation in vivo	Sobey et al. (1993)
Dog	Myocardial I/R	Allopurinol	Inhibition of XO activity by allopurinol resulted in a dose-dependent increase in cardiac interstitial fluid hypoxanthine and xanthine levels and a decrease in uric acid	Kuzmin et al. (1995)
Newborn lamb	Low O_2 ventilation and blood volume reduction-induced hypoxic injury	Allopurinol	Allopurinol exerted a beneficial effect on the pump function by afterload reduction but not by changes in contractility and also inhibited uric acid formation with a consequent decrease in antioxidative capacity	Shahid et al. (1999)
Pig heart	Myocardial I/R	Allopurinol, Oxypurinol	Decreased reperfusion injury, free radical scavenging effect	Das et al. (1987)
Pig heart and lung	I/R associated with heart-lung transplantation	Allopurinol	Better recovery of cardiac and pulmonary function and generalized alterations in tissue antioxidant status	Qayumi et al. (1993)
Pig	Myocardial I/R	Allopurinol	Better recovery of cardiac function and decreased propensity of reperfusion arrhythmias	Hopson et al. (1995)
Human (169 patients)	Coronary bypass surgery	Allopurinol	Decreased hospital mortality rate, increased cardiac index	Johnson et al. (1991)
Human (90 patients)	Coronary bypass surgery	Allopurinol	Reduced arrhythmias, need for inotropes and perioperative myocardial infarction in patients	Rashid and William-Olsson (1991)
Human (140 patients)	Myocardial I	Allopurinol	Increased incidence of infarct extensions in the treatment group	Parmley et al. (1992)*
Human (80 patients)	Ischemic heart disease	Allopurinol + erinit	Decreases in serum and daily urinary levels of uric acid and lipid peroxidation antioxidative system and an improvement of central hemodynamics	Kaliakin and Mit'kin (1993)
Human (50 patients)	Coronary bypass surgery	Allopurinol	Improves postoperative recovery and reduces lipid peroxidation in patients undergoing coronary artery bypass grafting	Coghlan et al. (1994)
Human (20 patients)	Coronary bypass surgery	Allopurinol	Failed to demonstrate a cardioprotective effect of allopurinol in patients with good left ventricular function undergoing elective coronary artery surgery	Taggart et al. (1994)*
Human (20 patients)	Coronary bypass surgery	Allopurinol	Allopurinol suppressed the reaction rate of xanthine oxidase; therefore, the levels of intermediates, hypoxanthine and xanthine, were high, and the level of the final product, uric acid, was low—however, allopurinol had no efficacy for the level of lactate, pyruvate, CK, and CK-MB	Yamazaki et al. (1995)*
Human (33 patients)	Coronary bypass surgery	Allopurinol	Better recovery of cardiac output and left ventricular stroke work	Castelli et al. (1995)

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
			after bypass surgery and reduction of plasma XO activity and concentrations of uric acid	
Human (52 patients)	Coronary bypass surgery	Allopurinol	Allopurinol failed to improve left ventricular stroke work after cardiopulmonary bypass surgery	Coetzee et al. (1996)*
Human (38 patients)	Percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction	Allopurinol	Allopurinol pretreatment was effective in inhibiting generation of oxygen-derived radicals during reperfusion and in the recovery of left ventricular function	Guan et al. (2003)

I/R, ischemia-reperfusion; I, ischemia; CK, creatine kinase.

*Studies concluded with negative results.

TABLE 2

Effects of XO inhibitors in cerebral, intestinal, liver, kidney and lung ischemia-reperfusion injury

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
Cerebral I/R				
Gerbil	Temporary unilateral carotid artery occlusion	Tungsten, Allopurinol	Tungsten and allopurinol protected against neurological deficits and damage	Patt et al. (1988); Phillis and Lin (1991)
Gerbil	Global brain ischemia induced by the ligation of both common carotid arteries	Oxypurinol	Oxypurinol failed to protect against ischemic brain damage	Arai et al. (1998) *
Rat	Occlusion of bilateral common carotid arteries in SHRs	Allopurinol	Allopurinol pretreatment reduced infarct size and prevented mortality	Itoh et al. (1986)
Rat	Permanent middle cerebral artery occlusion	Allopurinol	Allopurinol pretreatment reduced infarct size	Martz et al. (1989)
Rat	Transient MCA occlusion	Oxypurinol	Oxypurinol reduced the ischemic cerebral damage, increased cellular ATP levels, and attenuated the neurological deficits	Lin and Phillis (1991, 1992); Phillis and Lin (1991); Phillis et al. (1995)
Rat	Transient MCA occlusion	Oxypurinol	Oxypurinol failed to show any preventive effect on the infarction in contrast to other free radical scavengers	Nakashima et al. (1999) *
Rat	Permanent MCA occlusion	Allopurinol	Only very high doses of allopurinol pretreatment reduced the infarct size, which was independent of XO inhibition	Lindsay et al. (1991)
Newborn rats and lambs	Ligation of the right common carotid artery	Allopurinol	Allopurinol reduced both cerebral edema and the extent of perinatal hypoxic-ischemic brain damage	Palmer et al. (1990, 1993); Shadid et al. (1998)
Rabbit	Focal cerebral ischemia	Allopurinol	Allopurinol pretreatment protected neural tissue in the early period after arterial occlusion and prevented cerebral injury in the late period and also decreased uric acid levels	Akdemir et al. (2001)
Human	Severely asphyxiated infants	Allopurinol	Allopurinol tended to improve survival and exerted beneficial effects on free radical formation, cerebral blood flow volume, and electrical brain activity	Van Bel et al. (1998)
Splanchnic I/R				
Mouse	Intestinal I/R	Allopurinol	Allopurinol reduced the colonic leukocyte infiltration, rolling and adhesion, levels of lipid peroxidation, and inflammatory chemokines	Riaz et al. (2002, 2003)
Rat	Intestinal ischemia or I/R	Allopurinol, tungsten	Allopurinol reduced I/R-induced neutrophil infiltration and bacterial translocation	Grisham et al. (1986); Deitsch et al. (1988); Vaughan et al. (1992)
Rat	Intestinal I/R	Allopurinol	Allopurinol decreased mucosal injury and reduced mortality	Megison et al. (1990)
Rat	Intestinal I/R	Allopurinol	Allopurinol-induced increased survival in intestinal ischemia in rats was attributed to an effect unrelated to XO inhibition	Garcia Garcia et al. (1990)
Rat	Intestinal I/R	Tungsten	Protection against gut reperfusion injury	Pitt et al. (1991)
Rat	Intestinal I/R	Allopurinol	Administration of allopurinol before reperfusion preserved intestinal motility	Hakguder et al. (2002)

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
Cat	Intestinal ischemia	Allopurinol	Allopurinol attenuated the necrosis of villus and crypt epithelium and the pathologically increased vascular permeability	Parks et al. (1982); Parks and Granger (1983); Granger et al. (1986); Nilsson et al. (1994); Kulah et al. (2004)
Dog	Intestinal I/R	Allopurinol	Allopurinol reduced histamine release in the reperfused gut	Boros et al. (1989)
Dog	Intestinal I/R	Allopurinol	Allopurinol significantly elevated the postischemic 6-keto prostaglandin 1α/ thromboxane B2 ratio	Boros et al. (1991)
Liver I/R				
Mouse	Liver I/R	BOF-4272	BOF-4272 attenuated hepatic damage indicated by decreased hepatic enzyme release and lipid peroxidation during hypoxia reoxygenation	Kakita et al. (2002)
Rat	Liver ischemia or I/R	NA	Up-regulation of XO, the conversion of XO to XDH during ischemia	Engerson et al. (1987); McKelvey et al. (1988); Frederiks and Bosch (1996)
Rat	Liver I/R	BOF-4272	BOF-4272 reduced the release of chemoattractant in response to oxygen radicals reducible by Kupffer cells	Matsumura et al. (1998)
Rat	Liver I/R	Allopurinol	Allopurinol decreased I/R-induced lipid peroxidation and nuclear factor-κB activation	Matsui et al. (2000)
Rat	Liver I/R	Allopurinol	Allopurinol attenuated hepatic damage indicated by decreased hepatic enzyme release	Yildirim et al. (2002)
Kidney I/R				
Rat, rat kidney	Renal I/R	Allopurinol	Allopurinol improved morphology and renal function	Linas et al. (1990); Hestin and Johns (1999); Rhoden et al. (2000b)
Rat kidney	Repetitive renal I/R	Allopurinol	Allopurinol improved renal function after repetitive brief I/R in the isolated perfused rat kidney	Willgoss et al. (2003)
Dog	Renal I/R induced by transplantation	Allopurinol	Protection against kidney transplantation damage	Owens et al. (1974)
Lung I/R				
Rat lung	Lung I/R	Lodoxamide, allopurinol	Lodoxamide (1 mM) caused significant attenuation of postischemic lung injury in isolated rat lung model	Lynch et al. (1988); Okuda et al. (1993)
Rabbit lung	Lung I/R	Allopurinol	Allopurinol attenuated lung injury	Aiba et al. (1992)

I/R, ischemia-reperfusion; MCA, middle cerebral artery.

* Studies concluded with negative results.

TABLE 3

Effects of XO inhibitors in chronic heart failure

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
Mouse	Coronary ligation-induced HF	Allopurinol	Allopurinol doubled the survival and improved contractility and response to isoproterenol both in vivo and in isolated muscle; allopurinol also reduced the elevated XO activity in mice with heart failure	Stull et al. (2004)
Mouse	Coronary ligation-induced HF	Allopurinol	Allopurinol improved left ventricular contractile function, decreased ROS generation, attenuated LV cavity dilation, and reduced myocardial hypertrophy and fibrosis	Engberding et al. (2004)
Mouse	Transgenic model of cardiomyopathy	Allopurinol	Chronic treatment prevented myofibrillar protein oxidation and preserved cardiac function	Duncan et al. (2005)
Mouse	Acute heart failure	Allopurinol, oxypurinol	XO inhibitors improved ventricular function	Naumova et al. (2005)
Rat	Monocrotaline-induced right ventricular hypertrophy and failure model and HF- induced by coronary ligation	N.A.	Increase in myocardial XO levels	de Jong et al. (2000)
Rat	Coronary ligation-induced HF	Oxypurinol	Oxypurinol improved cardiac contractility and mechanoenergetic coupling in HF without affecting resting tension and intracellular Ca^{2+} transients	Kögler et al. (2003)
Rat	Coronary ligation-induced HF	Allopurinol	Both acute (5-day) and chronic (10-week) treatment with allopurinol improved LV hemodynamics; chronic treatment also prevented LV remodeling	Mellin et al. (2005)
Rat	Spontaneously hypertensive heart failure rat	Oxypurinol	4-week treatment restored cardiac structure and function	Minhas et al. (2006)
Dog	Pacing-induced HF	Allopurinol	Allopurinol decreases myocardial oxygen consumption and increases mechanical efficiency in dogs with pacing-induced HF; increased myocardial XO activity or levels and subsequent increases in oxidative stress in the failing hearts	Ekelund et al. (1999); Saavedra et al. (2002)
Dog	Pacing-induced HR	Allopurinol	Allopurinol had no effects on LV contractile function or adrenergic responsiveness in normal conscious animals; in pacing-induced CHF, allopurinol improved	Ukai et al. (2001)

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
Dog	Pacing-induced HF	Allopurinol	LV systolic function at rest and during adrenergic stimulation and exercise Allopurinol ameliorated increases in afterload and reductions in myocardial contractility during evolving HF, thereby preserving ventricular-vascular coupling	Amado et al. (2005)
Human (56 patients)	CHF	N.A.	In patients with CHF, elevated circulating uric acid levels correlate with inflammatory markers (e.g., TNF-α and ICAM-1)	Leyva et al. (1998)
Human (9 patients)	Idiopathic dilated cardiomyopathy	Allopurinol	Intracoronary administration of allopurinol resulted in an acute improvement in myocardial efficiency by diminishing oxygen consumption in the presence of standard supportive therapy	Cappola et al. (2001)
Human (19 patients)	CHF	Allopurinol	Allopurinol improved endothelial function	Doehner et al. (2002); Farquharson et al. (2002)
Human (1760 patients)	CHF	Allopurinol	High-dose treatment with allopurinol was found to beneficially affect survival, whereas low-dose allopurinol treatment actually appeared to increase mortality	Struthers et al. (2002)
Human (50 patients)	CHF	Allopurinol	3-month allopurinol treatment had no effect on excerise capacity but reduced B-type natriuretic peptide, a surrogate marker for prognosis in CHF	Gavin and Struthers (2005)
Human (405 patients multicenter)	CHF	Oxypurinol	Failed to show significant benefits	Cardiome Pharma Corp. (Vancouver, BC, Canada)

HF, heart failure; N.A., not applicable; TNF-α, tumor necrosis factor-α; ICAM-1, intercellular adhesion molecule-1.

TABLE 4

Effects of XO inhibitors on vascular dysfunction associated with hypercholesterolemia, atherosclerosis, hypertension, diabetes, and chronic heart failure

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
Rabbit	Hypercholesterolemia	Oxypurinol	Decreased vascular free radical production	Ohara et al. (1993); Mugge et al. (1994); White et al. (1996)
Human (60 patients)	Hypercholesterolemia and hypertension	Oxypurinol	Oxypurinol improved in vivo endothelial-dependent vasorelaxation in hypercholesterolemic but not hypertensive patients	Cardillo et al. (1997)
Rat	HHcy-induced by methhionine feeding	Oxypurinol	Impaired flow-mediated vascular responses of HHcy arterioles were prevented by oxypurinol	Bagi et al. (2002)
Rat	SHRs	N.A.	Increased XO activity in the hearts of hypertensive rats	Janssen et al. (1993)
Rat	SHRs	Tungsten	Increased XO activities in the mesenteric tissues of SHRs, and normalization of endothelial function and blood pressure in these animals after inhibition of XO activity by tungsten	Suzuki et al. (1998)
Rat	SHRs	Oxypurinol	Significantly higher uric acid levels in SHRs than in normal rats; oxypurinol decreased the blood pressure in SHRs but not in normal rats	Nakazono et al. (1991)
Rat	Dahl salt-sensitive hypertensive rats	Tungsten	Tungsten-rich diet lowered blood pressure in Dahl salt-sensitive hypertensive rats but not in salt-resistant rats	Swei et al. (1999)
Rat	SHRs	Allopurinol	Renal XO activity was increased and correlated with systolic blood pressure during growth in SHRs but not in WKY rats; allopurinol had a negligible effect on blood pressure but prevented hypertension-induced left ventricular and renal hypertrophy in SHRs	Laakso et al. (1998, 2004)
Rat	Oxonic acid-induced hypertension	Allopurinol	Allopurinol or uricosuric agent (benziodarone) prevented uricase inhibitor (oxonic acid)-induced hypertension	Mazzali et al. (2001)
Rat	Hypertensive double-transgenic rats harboring human renin and angiotensinogen genes (*dTGR*)	Oxypurinol	Preincubation with oxypurinol improved impaired endothelium-dependent vascular relaxation in rats with elevated angiotensin II levels	Mervaala et al. (2001)
Rat	Dexamethasone-induced hypertension	Allopurinol	Allopurinol reduced blood pressure in hypertensive rats and attenuated the increased XO levels in cremaster muscle	Wallwork et al. (2003)
Human (19 and 11 patients)	CHF	Allopurinol	Allopurinol improved endothelial function	Doehner et al. (2002); Farquharson et al. (2002)
Human (24 patients)	CHF	N.A.	Endothelium-bound xanthine-oxidase activity was increased by >200% in patients with CHF and inversely correlated with endothelium-dependent vasodilation	Landmesser et al. (2002)
Human (32 patients)	Hyperuricemia-induced	Allopurinol	3-month therapy with allopurinol improved	Mercuro et al. (2004)

Model	Disease or Trigger	Mode of XO Inhibition	Effects of XO Inhibition	Reference
			impaired endothelium-dependent flow-mediated dilation in hyperuricemic subjects	

N.A., not available; HHcy, hyperhomocysteinemia; WKY, Wistar-Kyoto.